

What Is Critical for Liver Surgery and Partial Liver Transplantation: Size or Quality?

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Major liver resections and partial orthotopic liver transplantation (OLT) have become established procedures in liver surgery; for many patients, these techniques offer the only curative option.¹ Yet, many patients develop postoperative complications because the remnant livers or grafts are too small or of poor quality to sustain sufficient organ function. This somewhat new and poorly defined phenomenon has been termed “small-for-size syndrome” (SFSS) to describe this scenario. The concept is, in fact, not a new one, because as early as the 1970s, Thomas E. Starzl described the complicated postoperative course of a young woman subjected to an almost 90% hepatectomy and who was subsequently characterized by prolonged hyperbilirubinemia, encephalopathy, and coagulopathy.² In an unconventional way for a review, we will start with three case reports to illustrate the scope and clinical relevance of SFSS after liver surgery and transplantation.

Abbreviations: CALI, chemotherapy-associated liver injury; CT, computed tomography; DOI, 2,5-dimethoxy-4-iodoamphetamine; EHPBA, European Hepato-Pancreatico-Biliary Association; GRWR, graft-to-recipient weight ratio; HCC, hepatocellular carcinoma; IHPBA, International Hepato-Pancreatico-Biliary Association; IL-6, interleukin-6; LDLT, living donor liver transplantation; MELD, Model for End-Stage Liver Disease; OLT, orthotopic liver transplantation; PTX, pentoxifylline; RLBW, remnant liver to body weight; SFSS, small-for-size syndrome; TNF, tumor necrosis factor.

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This article is dedicated to Thomas E. Starzl for his lifelong contribution to liver surgery and transplantation.

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Case 1: A 47-year-old healthy man, whose wife was listed for OLT due to a symptomatic nonresectable hemangioendothelioma of the liver, offered to be considered for living donor liver transplantation (LDLT). Following the standard work-up for this procedure, he underwent a right hemi-hepatectomy including the middle hepatic vein to serve as allograft for his wife. The remnant left hemi-liver was estimated by computed tomographic (CT) volumetry to weigh 450 g, i.e., around 32% of the whole liver. The ratio of the remnant liver weight to body weight (RLBW) was 0.65%. The donor had a difficult postoperative course developing mild encephalopathy and hyperbilirubinemia lasting 20 days peaking at 178 $\mu\text{mol/L}$ (10.4 mg/dL) by day five, and severe coagulopathy (prothrombin time <30%) that normalized by day 7. The donor eventually recovered fully, and was discharged in good general condition 22 days after surgery.

Case 2: A 42-year-old male was listed for OLT because of Child B cirrhosis (Model for End-Stage Liver Disease [MELD] score: 21) and a small (3 cm) hepatocellular carcinoma (HCC) related to hepatitis B virus infection. He received the right hemi-liver containing the middle hepatic vein from his wife (graft weighing 620 g), who had an uneventful postoperative course. The ratio of graft size in grams to her husband's body weight (80 kg) (graft-to-recipient weight ratio [GRWR]) was 0.7%. The postoperative period was complicated by encephalopathy, hyperbilirubinemia (up to 262 $\mu\text{mol/L}$, 15.3 mg/dL) for 2 weeks, and prolonged coagulopathy with a factor V level below 20% at day 4. As a result of the delayed graft function, the patient required intensive care unit treatment for 1 week before the liver graft function improved. He was able to be discharged in good general condition on postoperative day 21.

Case 3: A 58-year-old male presented with multiple colorectal liver metastases in the right hemi-liver as well as in segment II, III, and 10 months after resection of the primary rectal tumor followed by 5 cycles of chemotherapy containing Folfox and Avastin. A



Fig. 1. Multislice CT of a patient with multiple bilobar liver metastases. Preoperative volumetry predicted a future remnant liver (blue) accounting for 26% of the total liver volume. Metastatic lesions do not contribute to the total liver volume.

work-up including positron emission tomography and CT failed to identify extrahepatic metastases. A curative resection was considered, involving a right hemihepatectomy associated with wedge resections of the tumors located in the left hemi-liver. The estimated weight of the remnant liver after surgery was 320 g, reflecting 26% of the whole-liver volume and RLBW of 0.5% (Fig. 1). Postoperatively, the patient developed severe encephalopathy, large amounts of ascites, hyperbilirubinemia up to 300 $\mu\text{mol/L}$ (17.5 mg/dL), and persistent coagulopathy with a prothrombin time below 30%. He subsequently developed renal failure requiring replacement therapy by postoperative day 5 and pulmonary edema requiring reintubation. He died in the intensive care unit on postoperative day 13.

These three cases illustrate the wide spectrum and clinical impact of SFSS, which possibly represents the most serious complication after partial OLT and major hepatectomy. Preventing SFSS and understanding the underlying mechanisms may provide the most significant impact in improving outcome of many patients with liver diseases subjected to surgery or transplantation.

What Is Small-for-Size Syndrome?

The liver has the fascinating ability to sustain its function, even after major reduction of its parenchymal mass, and regenerates to its normal size within a few days.¹ However, there is a critical mass below which liver function cannot be preserved, leading to the widely used but poorly defined entity of SFSS, which is characterized by encephalopathy, coagulopathy, ascites, prolonged hyperbilirubinemia, and hypo-

albuminemia, and is often associated with renal impairment followed by pulmonary failure and ultimately death. A few attempts were made to standardize the definition of SFSS to enable meaningful comparisons over time and among different institutions. At this point, however, no consensus has been reached, making comparisons of studies in the literature nearly impossible.

We previously attempted to define SFSS³ by the presence of two of the following three factors (bilirubin $>100 \mu\text{mol/L}$ [5.85 mg/dL], international normalized ratio >2 [prothrombin time $\sim 33\%$], and the presence of encephalopathy $\geq$ grade 3) on 3 consecutive days over the first postoperative week. SFSS should be, of course, considered only after exclusion of other causes of liver failure such as technical problems including outflow obstruction and immunological or infectious complications. Another definition, nicknamed “fifty-fifty criteria”, was designed to predict liver failure and death of patients after liver resection, and is defined by a prothrombin time $<50\%$ of normal along with a total bilirubin level $>50 \mu\text{mol/L}$ (2.9 mg/dL) on postoperative day five.⁴ This score was further validated prospectively in a series of patients after liver resection, by showing that 70% of patients who died postoperatively fulfilled the “fifty-fifty criteria”.⁵ This score was a strong predictor of death on multivariate analysis (odds ratio = 29.4; 95% confidence interval = 4.9-167). An important limitation of this system is its availability for prediction at the earliest 5 days after surgery. A third definition predicting the degree of postoperative hepatic dysfunction⁶ was based on selective parameters including bilirubin, prothrombin time, serum lactate levels, and the degree of encephalopathy. Each of these parameters was given 0-2 points, when changes were observed for at least 2 consecutive days. An appealing aspect of this approach is that the degree of liver failure can be calculated at any time during the postoperative course. The grouping of the score into none, mild, moderate, or severe hepatic dysfunction was shown to correlate with the size of the remnant liver (Fig. 2).

What Is the Minimum “Safe” Amount of Liver After Surgery and Partial OLT?

The size of the remnant liver is a major determinant of postoperative liver failure, and logically depends on the quality of the liver parenchyma, or in other words, the presence of underlying liver diseases. The impact of underlying liver conditions will be discussed below, and we will focus here on the ideal scenario of patients

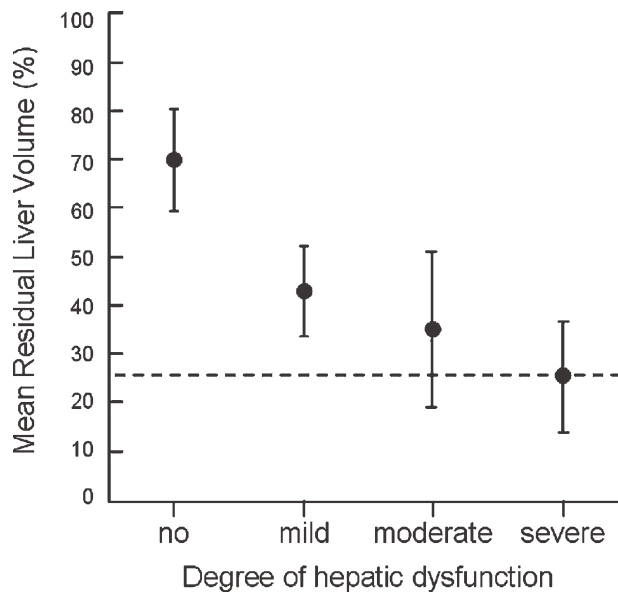


Fig. 2. Mean residual liver volume after liver resection grouped by patients either without or with mild, moderate, and severe hepatic dysfunction. Dotted line indicates calculated critical remnant liver volume of 27%. (Adapted from Schindl et al.⁶)

presenting without significant risk factors. We tried to determine the minimal amount of remnant liver mass compatible with acceptable postoperative function and survival through a survey including 100 international well-established liver centers identified through the memberships to two specialized societies in the field: the IHPBA (International Hepato-Pancreatico-Biliary Association) and EHPBA (European Hepato-Pancreatico-Biliary Association).⁷ The results indicated that most experienced liver surgeons consider 25% (range: 15%-40%) of the remnant liver mass (RLBW: 0.5) as their limit for liver resections. Transplant surgeons, on the other hand, use significantly higher figures, with a GRWR of at least 0.8% (range: 0.6-1.2) which corresponds to 40% of the transplanted total liver volume. The lowest figure of 0.6% should be used only when the graft is implanted in a recipient without cirrhosis or with cirrhosis, but well-preserved liver function (Child A and low MELD score).⁸ This discrepancy between the critical liver mass needed after liver resection (~25%) and partial OLT (~40%) remains unclear. Part of the explanation may include exposure to cold ischemia, immunosuppressants, denervation of the graft, as well as host factors such as changes in vascular flow due to preexisting portal hypertension. Yet, it is unclear which of these factors contribute most to the requirement for a larger mass after OLT, when compared to resection only. Of note, the survey disclosed a minimal residual volume of 50% (range: 25%-90%) after resection in the population of patients

with cirrhosis, highlighting the negative impact of pre-existing disease.^{7,8}

A few authors have correlated the extent of liver resection with subsequent postoperative outcome.^{6,9-13} Two reports demonstrated a dramatic increase in the rates and severity of complications after major resections with remnant livers < 20%,^{12,13} whereas the group from Edinburgh,⁶ using the score mentioned above, proposed a safety cutoff of 27% for the remnant liver mass (Fig. 2). In transplantation, a number of studies have suggested that grafts should be considered for LDLT only if the GRWR is higher than 0.8,¹⁴⁻¹⁷ which explains the consistent reply in the survey, and the wide acceptance of this lower limit.⁷

How Does Quality of the Liver Parenchyma Affect Outcome of Major Liver Resection and Partial OLT?

Many risk factors are incriminated to affect outcomes in liver surgery and transplantation (Table 1). Because of space limitation, we will focus on age, liver steatosis, and exposure to chemotherapy, because those are frequently encountered in our patients.

How Do "Older" Livers Tolerate Liver Surgery and Partial OLT?

Strong evidence from basic¹⁸⁻²¹ as well as clinical^{22,23} studies exist that liver regeneration is impaired in old livers. The underlying mechanisms have only been partially identified. Down-regulation of several key molecules during aging ultimately lead to changes in several cyclins, that arrest cells in the cell cycle. Growth hormone seems to reverse these age-associated alterations.^{20,21} In a rodent model, old animals demonstrated delayed regeneration after partial hepatectomy, which could be corrected to the range of young animals by the addition of growth hormone. This treatment activated cyclin-dependent kinases and down-regulated its inhibitors, enabling the progression in the cell cycle which is required for liver regeneration.

Table 1. Risk Factors for SFSS

• Age
• Steatosis
• Steatohepatitis
• Hepatitis
• Intraoperative blood loss
• Ischemia
• Obstructive cholestasis
• Preoperative chemotherapy
• Fibrosis
• Cirrhosis

In a study in patients who have undergone LDLT, serial volumetric analyses showed delayed liver regeneration in older donors. Donors older than 50 years of age disclosed significantly smaller volumes 1 week after resection compared to young (<30 years) individuals. However, volume eventually returned to normal sizes by 1 month after resection.²²

Not only the regenerative capacity decreases with age, but also liver volume²⁴⁻²⁶ and liver hepatic microcirculation.²⁷ In addition, a so-called "pseudocapillarization"²⁸ of the sinusoids has been observed with advancing age which consists of a thickening of the endothelial lining and loss of the fenestrae.²⁹ This combination may explain the known impaired clearance of a number of drugs in the elderly population.^{30,31} Although speculative, this might also influence liver regeneration. Despite all these changes, the liver architecture seen in conventional histological examination does not differ between young and old individuals.^{32,33}

In experimental studies, older mice were found to be more susceptible than younger animals to ischemic injury, which is related in part to a loss in energy stores, i.e., glycogen and adenosine triphosphate.³³ Some protective strategies in young animals, such as ischemic preconditioning, were no longer effective in older animals, but protection could be restored by reloading the energy stores with glucose.³³ This finding was confirmed in a prospective randomized controlled study that tested the effect of ischemic preconditioning in patients undergoing liver resection. Patients above the age of 65 years did not benefit from the protective effect of preconditioning.³⁴

Despite the aforementioned limitations, several studies failed to show that advanced age affects the outcome of patients undergoing a variety of surgical procedures³⁵⁻³⁷ including liver surgery.^{22,38,39} Yet, age has to be considered a significant risk factor for major liver resection and partial liver transplantation.^{1,40}

Does Steatosis of the Liver Affect Surgical Outcomes?

Many studies have shown that steatosis, particularly severe steatosis, is a significant risk factor for postoperative complications after major liver resection,⁴¹⁻⁴³ and exerts detrimental effects on graft and patient survival after OLT.⁴⁴⁻⁴⁸ In contrast, other studies failed to identify any negative effects.⁴⁹⁻⁵³ These discrepancies have led to many uncertainties in this field.

Hepatic steatosis is defined as excessive lipid accumulation that exceeds 5%-10% of the organ weight.⁴³ In clinical practice, microscopic assessment of fat droplets in hepatocytes, mostly on sections stained with hematox-

ylin and eosin, represents the gold standard by which to characterize hepatic steatosis. Quantitative assessment is recorded as the percent of hepatocytes containing lipid droplets (mild steatosis: <30%; moderate: 30%-60%; and severe >60%), whereas qualitative assessment takes into account the size of the droplets in hepatocytes.^{54,55} If the lipid droplets displace the nucleus, it is considered macrosteatosis, otherwise the term microsteatosis is used. Many pitfalls have been demonstrated with this approach, including errors due to liver sampling,⁵⁶ the inhomogeneous distribution of lipids throughout the liver,⁵⁷ and fixation and staining of liver sections.^{45,58}

In addition, we recently showed poor agreement among expert pathologists from different institutions in assessing steatosis, both quantitatively and qualitatively, in the same liver sections.⁵⁹ For example, one pathologist diagnosed 22% of patients with marked ($\geq 30\%$) steatosis, whereas another recorded an incidence of 46%. Also, significant disagreement was documented regarding many features of steatohepatitis.⁵⁹

The actual types and contents of fat in the liver are most likely more relevant to predict outcome after surgery and transplantation than the amount.^{54,60,61} The distinction between microsteatosis versus macrosteatosis might be artificial, because continuity exists between both forms of fat.⁵⁴ For example, in a mouse model, the chemical composition of hepatic lipids best predicted the degree of injury following an ischemic insult,⁵⁴ and the microcirculatory failure following reperfusion correlated with reduced hepatic content of Ω -3 fatty acids and a nonphysiologically high Ω -6 : Ω -3 fatty acid ratio.⁶⁰ Pretreatment with dietary Ω -3 fatty acids reduced total hepatic lipid content, with conversion of the predominant histological pattern of macrosteatosis into microvesicular steatosis, improved sinusoidal perfusion, and decreased hepatocellular damage after reperfusion.⁵⁴

In humans, prolonged Ω -3 fatty acid supplementation to patients with liver steatosis improved the biochemical and ultrasonographic features of fatty liver.⁶² Recently, we treated three candidates for LDLT, who presented with biopsy-proven hepatic macrosteatosis > 30%, with oral Ω -3 fatty acids. Steatosis decreased significantly in each case within 1 month of diet supplementation, and a successful LDLT could be performed (Fig. 3) (A.M. El-Badry, P.A. Clavien; unpublished data).

Does Chemotherapy-Induced Liver Injury Adversely Affect Outcomes in Liver Surgery?

An increasing body of evidence suggests that the use of a variety of neoadjuvant or perioperative

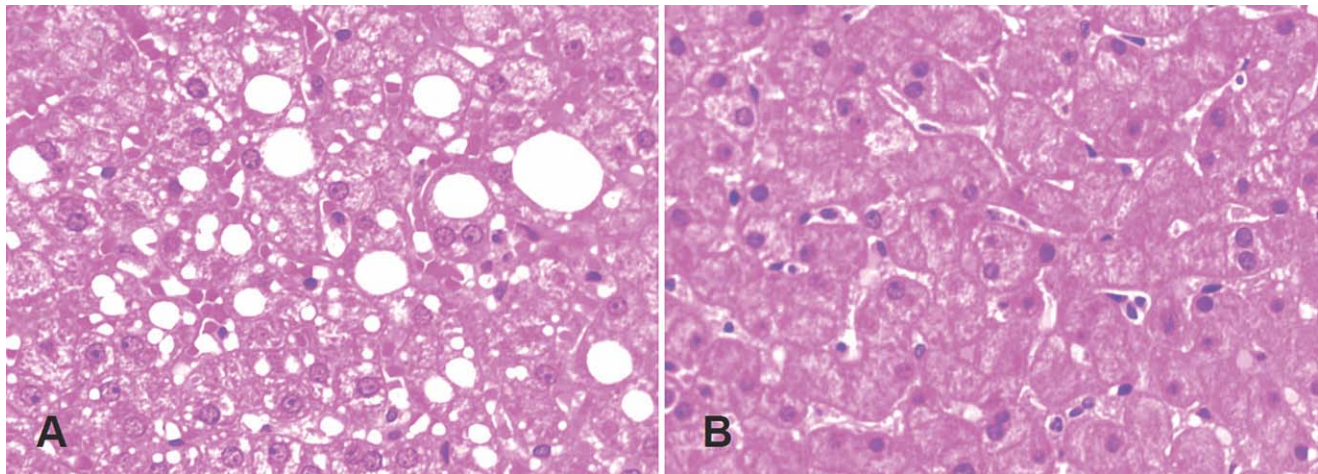


Fig. 3. Representative hematoxylin α eosin stained liver sections (400 $\times$) obtained from a candidate for living donation of the right hemi-liver demonstrating (A) moderate infiltration of hepatocyte by lipid droplets that was (B) dramatically reduced within 1 month of oral Ω -3 fatty acid administration (dosage: 1.5 g/day).

chemotherapeutic drugs in patients with colorectal liver metastases improved long-term survival after liver resection.⁶³⁻⁶⁵ However, concerns exist regarding hepatic injury related to these agents, termed chemotherapy-associated liver injury (CALI). The exact incidence and the relevance of the risk factor for major hepatectomy remains controversial, but appear highly dependent on the types of drugs used and the duration of treatment.⁶⁶

Some drugs have been associated with specific types of injury, for example, the use of 5-fluorouracil and irinotecan (CPT 11) may cause steatosis and steatohepatitis, whereas oxaliplatin is associated with an entity called sinusoidal obstruction syndrome⁶⁷ (Table 2). The causative molecular events associated with 5-fluor-

ouracil and irinotecan hepatotoxicity include oxidation of fatty acids and mitochondrial damage with further production of reactive oxygen species, leading to the inability to metabolize substances such as lipids.^{68,69} Oxaliplatin-induced sinusoidal obstruction syndrome has been associated with the depletion of glutathione from sinusoidal cells secondary to the production of exaggerated oxidative stress⁷⁰ (Fig. 4).

In current practice, patients are usually treated with a cocktail of drugs, which may induce synergistic toxicities.⁷¹ Several factors may enhance the toxicity of chemotherapeutic regimens such as hyperglycemia, obesity, and older age, whereas aspirin may be protective.⁷² Most liver surgeons will call for caution in treating patients exposed to long and extensive chemotherapy.

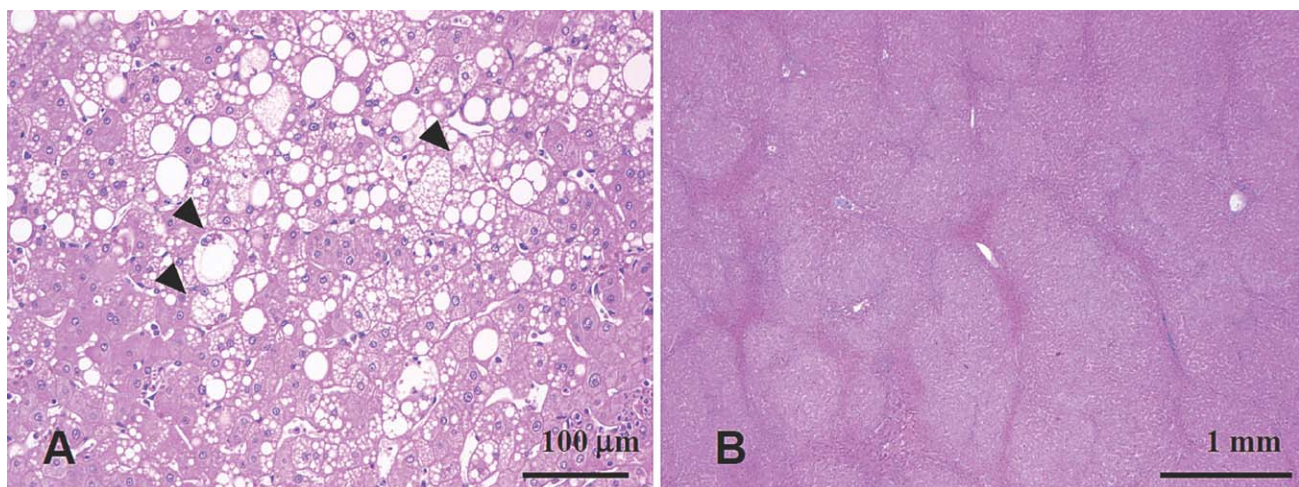


Fig. 4. Hepatic changes following long-term therapy with chemotherapeutic agents result in a typical pattern of liver injury. (A) Microvesicular and macrovesicular steatosis with hepatocyte ballooning and Mallory bodies (arrows) is observed after treatment with irinotecan (chemotherapy-associated steatohepatitis). (B) Profound nodular regenerative hyperplasia with nodules outlined by congested areas (darker areas) is observed after treatment with oxaliplatin (sinusoidal obstruction syndrome).

Table 2. Patterns of CALI and Impact on Outcomes

Patterns of Parenchymal Damage	Drugs Implicated	Type of Study	Impact on Outcomes	Weight of Evidence
Steatosis	5-fluorouracil and leucovorin	Case-controlled studies and retrospective review	Increased morbidity—mainly infectious complications	Independent prognostic factor on multivariate analysis in single-center case-controlled studies (Levels III and IV)
Sinusoidal obstructive syndrome	Oxaliplatin	Case-controlled studies and retrospective review	Increased morbidity and blood transfusion requirement	Evidence based on case-controlled studies and retrospective review (Levels III and IV)
Steatohepatitis	Irinotecan	Case-controlled studies	Increased morbidity and 90-day mortality	Independent prognostic factor on multivariate analysis in case-controlled studies (Level III)
Extrahepatic biliary sclerosis	Intra-arterial floxuridine	Case-controlled studies and retrospective review	Long-term biliary damage—usually permanent	Evidence from case-controlled studies and retrospective review (Levels III and IV)

Obtained with permission from Khan et al.¹³⁴

Data assessing the risk are scarce. Several studies have failed to identify an additional risk, whereas others reported increased morbidity in up to 23% of the cases^{42,63,73,74} and even increased mortality⁶⁶ (Table 2).

The impact of chemotherapy on liver regeneration also remains unclear due to the lack of an animal model of CALI and the limitation of endpoints for liver regeneration in clinical studies. Most studies did not show a negative impact on regeneration,⁷⁵ whereas a recent study demonstrated an impaired regeneration following portal vein embolization in patients subjected to chemotherapy.^{76,77}

What Are the Underlying Mechanisms of SFSS?

The mechanisms of SFSS, particularly in the presence of an underlying liver disease, remain largely unknown. The first step to get insights into the mechanisms and molecular pathways involved in SFSS is the availability of a convincing animal model. A few years ago, we developed a model of OLT in the mouse, which, contrarily to the rat model, required reconstruction of the hepatic artery for full recovery.⁷⁸ More than half of the animals in which the hepatic artery was not connected developed major bile duct injury plus large areas of hepatocyte necrosis with ensuing death of most animals within a few days after OLT. In contrast, all animals with reconnection of the hepatic artery enjoyed long-term survival.⁷⁹ We subsequently developed a partial liver graft model that mimicked the clinical scenario of SFSS. A small graft obtained by harvesting the middle lobe only, i.e., ≈30% of the total liver volume, consistently induced primary nonfunction of the graft and animal death, whereas all animals receiving a 50% graft survived.⁷⁹

In the failing small grafts, we observed the development of hepatocyte ballooning, microvesicular steatosis, and, surprisingly, an almost complete failure of hepatocyte proliferation (Fig. 5). Similar findings were noted in the human cases of primary nonfunction after OLT. These findings led to the hypothesis that defective liver regeneration is the central mechanism of SFSS. Similar models of SFSS following extensive liver resection (e.g., 90% hepatectomy in rodents) disclosed similar patterns of impaired regeneration,^{80,81} including ballooning and the development of a diffuse form of microsteatosis.⁸² In contrast to transplantation, these latter models do not include warm ischemia and therefore exclude the inflammatory cascade of ischemia/reperfusion injury. Yet, the common feature appears to be inability of those small livers to regenerate. The focus therefore should turn toward the relevant pathways of regeneration involved in SFSS.

The orchestra of cells, growth factors, or intracellular signaling pathways leading to liver regeneration are complex, only partially identified, and have been well summarized in a number of recent review articles (Fig. 6).^{1,83,84} An important credit should be given to Thomas E. Starzl, who performed pioneering studies in dogs that demonstrate the importance of portal flow with the discovery of the mitogenic effects of growth factors such as insulin.²

Although a comprehensive review on pathways of liver regeneration is out of the scope of this article, a few relevant mechanisms deserve attention. Liver regeneration in many *in vivo* models appears to be initiated by an inflammatory cascade involving endotoxins⁸⁵ and a number of acute phase proteins such as interleukin-6 (IL-6),⁸⁶ tumor necrosis factor alpha (TNF α),⁸⁷ or complement factors.⁸⁸ In a series of experiments that tested the role of acute phase proteins

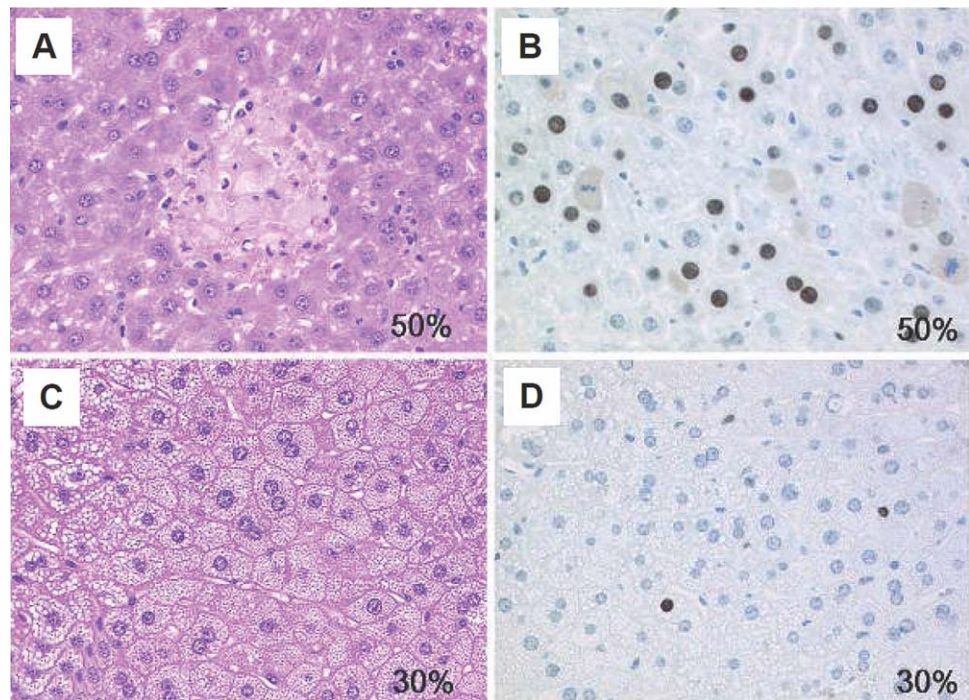


Fig. 5. Failure of liver regeneration is a central mechanism of SFSS. At 48 hours after transplantation, a 50% graft exhibits (A) minor tissue injury, including (B) only few foci of necrosis. In this graft, regeneration is completely preserved. In contrast, the 30% graft displays (C) microvesicular steatosis and (D) a blunted regeneration. (Adapted from Tian et al.⁷⁹)

in our model of partial (30% graft) OLT in mice, we found that pentoxifylline (PTX) rescued the failure of regeneration and restored animal survival.⁸⁹ PTX was found to confer its protective effects through enhanced production of IL-6, while down-regulating TNF α production, because the protective effects of PTX was lost

in IL-6 knockout mice. This data also indicated that IL-6 acts downstream to TNF α and that inhibition of TNF α , possibly resulting from the ischemic injury, might also be beneficial in this model. Similar data are available following extensive hepatectomy, i.e., in the absence of the associated insults inherent to OLT such

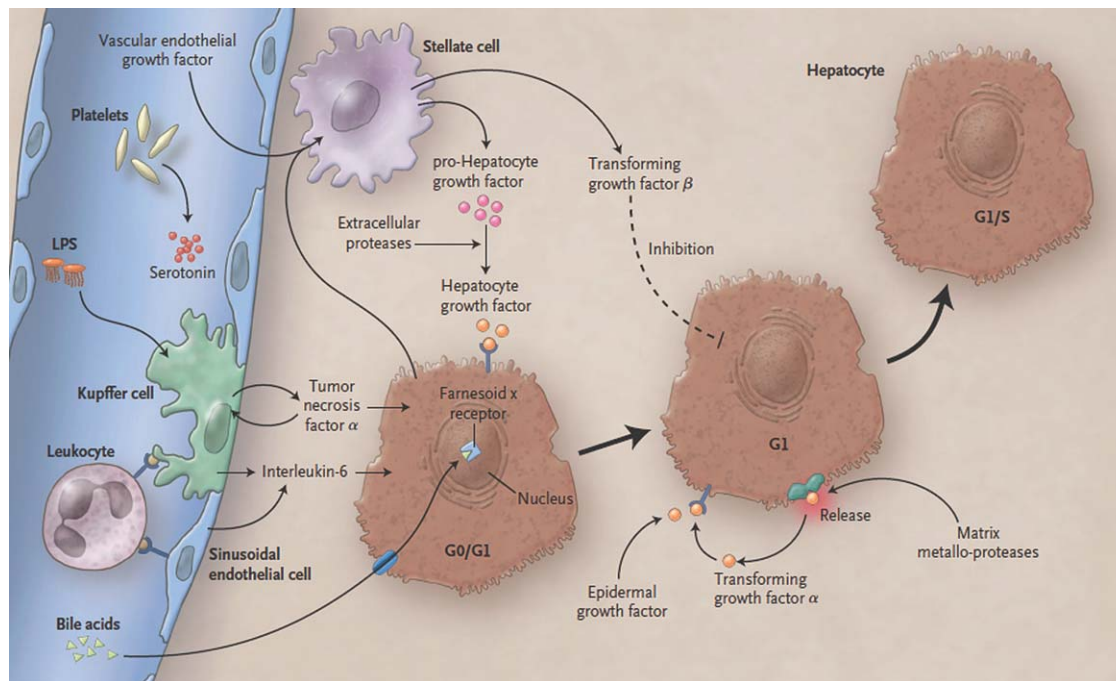


Fig. 6. Mechanisms of liver regeneration after hepatic resection (adapted from Clavien et al.¹). This illustration demonstrates the complexity of factors involved in liver regeneration involving bloodborne cells as well as soluble factors that interact with parenchymal and stromal cells of the liver.

as ischemia/reperfusion injury. For example, IL-6 or the endogenous receptor agonist cardiotrophin-1 rescued hepatocyte proliferation and animal survival in rodent models of 90% hepatectomy⁸² or ischemia/reperfusion injury.⁹⁰ However, chronic exposure to the cytokine IL-6 may cause deleterious effects by increasing proapoptotic proteins (Bax).⁹¹ Similar effects were documented for complement, which was permissive and protective only in a balanced low dose, but induced damage at higher doses.⁹² We conclude from these observations that there seems to be a labile equilibrium for acute phase cytokines during the initial phase of liver regeneration. Although regeneration cannot be triggered in the absence of these molecules, their excess may contribute to organ failure in the situation of extensive tissue loss or the presence of underlying pathological conditions such as steatosis.

Platelet-derived serotonin has recently been identified as a major contributing factor to liver regeneration.⁹³ In a first set of experiments, antibody-mediated thrombocytopenia or various pharmacological inhibitions of platelet actions impaired liver regeneration. To identify the critical component in platelets, mice lacking a rate-limiting enzyme (tryptophan hydroxylase-1) involved in the early step of peripheral serotonin biosynthesis, displayed blunted liver regeneration after hepatectomy. This defect was corrected with the use of 5-hydroxy tryptophan, a precursor of serotonin which does not require the action of tryptophan hydroxylase-1. In addition to the use of 5-hydroxy tryptophan receptor agonist 2,5-dimethoxy-4-iodoamphetamine (DOI) restored regeneration in mice deficient in tryptophan hydroxylase-1.⁹³

Similar results were observed in our model of partial (30%) OLT. The use of DOI reversed the failure of hepatocyte proliferation and rescued animal survival.⁹⁴ These effects appeared independent from the IL-6 pathway, i.e., from the protective effects of PTX. Others found that thrombocytosis enhances hepatocyte proliferation in mice subjected to extended hepatectomy, a mechanisms possibly related to signaling pathway involving signal transducer and activator of transcription 3 (Stat3) and Akt.⁹⁵ However, IL-6 and serotonin were not investigated in this study.

It was previously shown in a variety of rodent models that platelets contribute to warm⁹⁶ and cold⁹⁷ ischemic injuries. Thus, serotonin might also cause injury in models combining hepatectomy and an ischemic insult such as transplantation. In a series of experiments, we failed to show any negative impacts of serotonin following ischemia/reperfusion injury in the liver, but rather documented a beneficial effect in promoting tissue repair following the ischemic insult.⁹⁸

The mechanism through which serotonin enhances regeneration is not yet fully clarified. Serotonin may directly act on hepatocytes as a mitogen or may evoke also indirect effects by improving hepatic microcirculation, particularly in the aged liver (P.A. Clavien; unpublished data) or by balancing the acute phase protein reaction by nonparenchymal cells. Those questions are the focus of current research in a number of laboratories.

Is the Hyperperfusion Theory Observed by Surgeons Relevant?

The finding by surgeons of increased pressure and flow in the portal vein after partial OLT, particularly in small grafts, has led to the theory of mechanical and overperfusion types of injury involving the hepatic microcirculation.⁹⁹⁻¹⁰¹ Denudation of the endothelium lining of sinusoids may lead to focal hemorrhage into connective tissue of the portal tract, consequently impairing hepatic microcirculation, causing congestion and with subsequent hepatocyte necrosis and liver failure.^{102,103} On top of this, the buffer effect of increased portal flow causing decreased flow in the hepatic artery, which was well described many years ago,¹⁰⁴ is preserved after partial OLT.¹⁰⁴⁻¹⁰⁶ Thus, high flow and pressure in the portal vein after partial OLT may mediate major injury through poor flow in the hepatic artery.¹⁰⁷

This theory was tested in a few patients after LDLT. Dr. Boillot in Lyon, France, described a 55-year-old recipient who received a left hemi-liver weighing 430 g corresponding to a GRWR of 0.6%, in whom he performed a mesocaval shunt to decompress the portal system (Fig. 7A).⁹⁹ The postoperative course was uneventful with normal serum aminotransferases and bilirubin levels within 5 days. A number of strategies have been developed with the same aim to decompress the portal system. For example, construction of a portocaval shunt connecting a branch of the portal vein of the graft¹⁰⁸ to the circulatory system, or the use of transient portocaval shunts for a few days following surgery,¹⁰⁹ may provide benefits (Fig. 7B). The inherent risk is a "too effective" diversion of the portal blood to the systemic circulation with a risk of graft failure through a stealing mechanism that causes decreased portal flow. To circumvent such a risk, other strategies have been designed such as splenic artery ligation or embolization.¹⁰⁹⁻¹¹² The rationale of this procedure is to cause an increased pressure and flow in the hepatic artery with a concomitant slight decrease of the portal flow. A beneficial effect has been suggested in a small case series of eight patients.¹⁰³

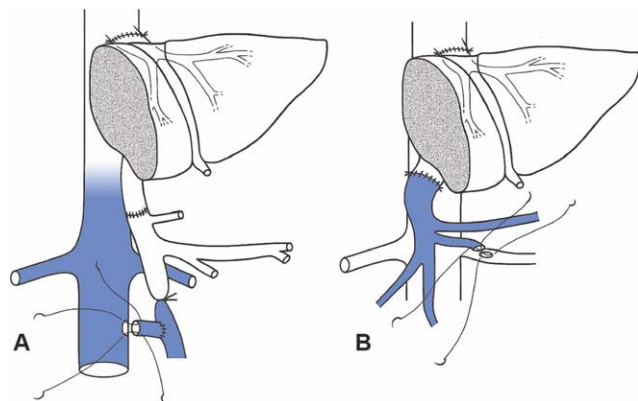


Fig. 7. Two different shunting techniques to prevent hyperperfusion of the graft^{99,108}. Illustration in (A) shows a mesocaval shunt by using an iliac vein graft and ligation of the superior mesenteric vein downstream from the shunt; the superior mesenteric venous outflow is totally diverted into the inferior vena cava.⁹⁹ Illustration in (B) shows a mesorenal shunt with an end-to-side anastomosis of the inferior mesenteric vein and left renal vein.¹⁰⁸

In contrast to these somewhat convincing surgical observations, several reports provided data challenging this “hyperperfusion theory”. A series of small grafts (GRWR <0.8%) were successfully used without any attempt at a decompression of the venous system.¹⁴ Other researchers¹¹³ compared patients who received large versus small grafts. Both reports failed to identify any differences in outcome, suggesting that a high portal flow is of little relevance. The group of S. T. Fan, in Hong Kong, China, recently suggested that the limiting factor is at the level of the outflow (hepatic veins) rather than the inflow (portal vein).¹¹⁴ In a study including 46 LDLT recipients, they did not observe any correlation between portal inflow, portal pressure, and SFSS. The authors explained this observation by the routine inclusion of the middle hepatic vein for the right hemi-liver grafts. Despite the use of a number of grafts with GRWR <0.8%, only one patient disclosed signs of moderate sinusoidal congestion¹¹⁴ (Fig. 8).

These results lead to the conclusion that the protective effects of interventions leading to decompression of the portal system are only useful in the presence of an outflow impairment. However, the definition of SFSS requires that technical problems are excluded. Therefore, we propose that the “portal hyperperfusion theory” should not be a feature of SFSS.

Protective Strategies

In this section, we will cover a variety of proven and promising protective strategies to prevent and treat SFSS after major liver resection and partial OLT. Sev-

eral strategies apply only to one of the procedures, whereas others may confer benefits in both hepatectomy and transplantation. There is strong evidence that impaired regeneration is the major mechanism leading to SFSS in animal models as well as in humans. Therefore, most of the strategies target on liver regeneration.

What Are the Strategies to Increase Liver Size and Function?

Some novel strategies are available to increase volume and function of the potential remnant liver (also called future remnant liver) in patients who will undergo major liver resection. It is well-described that selective occlusion of a portal branch causes atrophy of the hepatic territory supplied by this vein and hypertrophy of the contralateral part.¹¹⁵ Atrophy of the occluded hemi-liver occurs through an increased apoptotic activity, whereas hypertrophy of the nonoccluded lobe is due to increased hepatocyte proliferation (hyperplasia).

Interruption of a portal branch can be achieved by several methods such as selective embolization by a radiology-guided transhepatic approach,¹³ or by surgical ligation. In most cases, occlusion is performed at the right portal vein in preparation for a right or extended right hemi-hepatectomy, if the potential left liver remnant is thought to be too small.^{1,115-117} Most surgeons consider a major resection about 4 weeks after portal vein occlusion.¹¹⁸ Portal vein embolization is also increasingly used as a dynamic preoperative test to

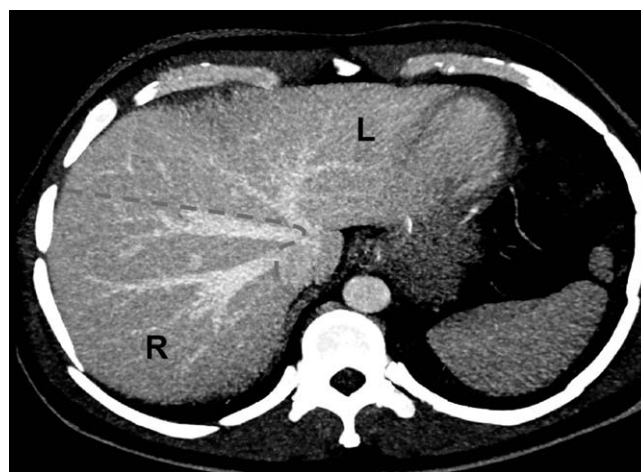


Fig. 8. Preoperative imaging of a healthy individual before living related liver donation. The right hemi-liver (R) is used as a graft, including the right and middle hepatic vein (dotted line). This strategy prevents venous outflow obstruction. The left hemi-liver (L) remains in the donor.

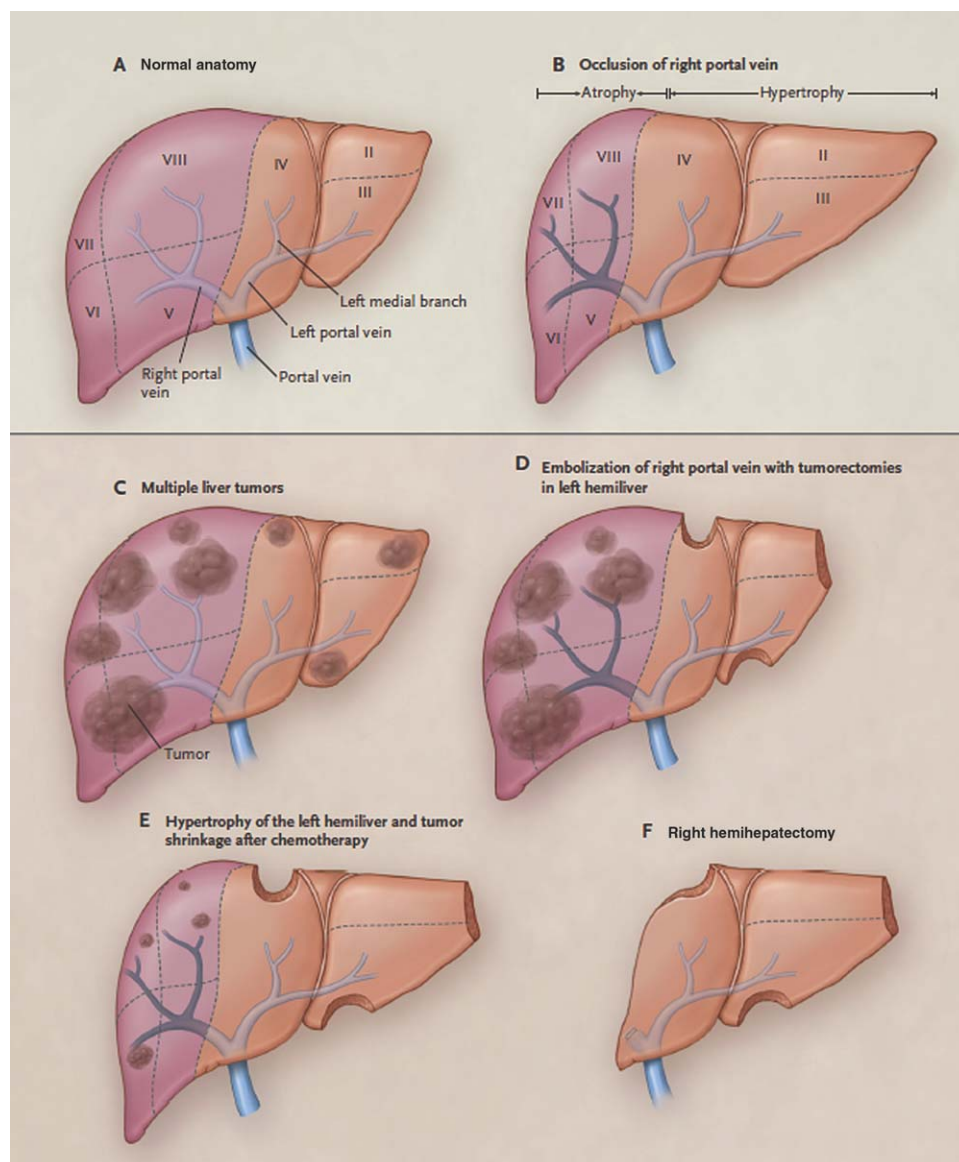


Fig. 9. Normal liver anatomy and the principle of portal vein occlusion and two-stage procedure. (A) Normal liver anatomy is shown, with segments II through VIII. Segment I, which lies posteriorly, next to the vena cava, is not shown. (B) Occlusion of the right portal vein is shown, which results in ipsilateral atrophy of the right hemi-liver (segments V through VIII) and contralateral compensatory hypertrophy of the left hemi-liver segments I through IV. (C) Metastases are shown throughout the liver. Panels (D), (E), and (F) show a two-stage procedure. In the first stage, small tumorectomies in the potential left remnant hemi-liver and occlusion of the right portal vein by means of portal vein embolization or ligation are performed. (D) A shrinkage of the right hemi-liver after right portal vein occlusion is shown, with compensatory hypertrophy of the contralateral hemi-liver. (E) In the second stage, a curative liver resection (right hemi-hepatectomy, segments V through VIII, or extended right hemi-hepatectomy, including segment IV) is performed (F). Obtained with permission from Clavien et al.¹

identify patients in whom liver regeneration is thought to be impaired; these patients should not undergo major hepatectomy.¹ This approach is especially relevant for patients presenting with underlying liver changes such as cholestasis, chronic liver diseases, and a history of chemotherapy.¹¹⁹

The manipulations of liver volume offer the possibility of curative surgery in many patients presenting with bilateral tumors. This is best achieved through the so called “two-stage procedure”¹ (Fig. 9). The most common scenario for the first stage consists of resection of all metastases in the left hemi-liver combined with a right portal-vein ligation¹ or embolization.¹²⁰ In the second stage, usually conducted 4 weeks later, a right or extended right hemi-hepatectomy is performed to achieve a curative (R0) resection. When concomitant systemic¹²¹ or intra-arterial chemother-

apy⁷⁵ is used, definitive liver resection is usually performed 3 or more months later.¹

Are Drugs that Enhance Regeneration or Prevent Ischemia/Reperfusion Injury Available?

Many drugs have been shown in a variety of animal models to protect small remnant livers after partial hepatectomy or OLT, yet none has reached the clinic; in fact, only a few have been tested in clinical trials.¹²² Antioxidants, caspase inhibitors, adenosine agonists, nitric oxide donors, protease inhibitors, prostaglandins, matrix metalloproteinase inhibitors, PTX, and Ω -3 fatty acids⁶⁰ are among the best candidates.¹²² A comprehensive review of the potential mechanisms of those drugs is beyond the scope of this review. We recently tested

PTX in a series of 100 patients who underwent major liver resection, and documented a benefit in patients presenting a RLBW <1.2.¹²³ Other drugs were shown in clinical trials to confer protection against ischemic injuries. For example, a pancaspase inhibitor lowered postoperative aminotransferase levels after OLT.¹²⁴

Another widely investigated strategy is ischemic preconditioning consisting of a short period of inflow occlusion (Pringle maneuver) and reperfusion followed by the prolonged ischemia during which the transection of the liver can be performed.¹²⁵ Although, as for the pancaspase inhibitor study, a significant lowering of aminotransferase levels was observed postoperatively after liver surgery³⁴ and OLT,¹²⁶ no relevant benefits on the postoperative course could be identified.¹²⁷ Currently, most surgeons use intermittent inflow occlusion in selective patients undergoing major liver resection.^{120,128} This strategy effectively prevents blood loss, while preserving the postoperative function of the liver, but so far no impact has been shown on liver regeneration. At best, this strategy may achieve similar results as major surgery performed without inflow occlusion and without blood loss.¹²⁰

Of interest, a novel approach involving pharmacological preconditioning with the volatile anesthetic sevoflurane given 30 minutes prior to liver resection, and tested in a randomized trial including more than 100 patients, was shown to dramatically ameliorate the postoperative outcome.¹²⁹ Not only surrogate markers of injury such as postoperative aminotransferase levels were lower, but the total number of complications, as well as the number of severe complications, were significantly decreased.¹²⁹ Sevoflurane appears to confer its protective effects through the nitric oxide pathway.^{130,131} Such a strategy would also be available for OLT with evidence that activation of the nitric oxide pathway is likewise of benefit.¹³² We have initiated a multicentric randomized study to test sevoflurane in liver transplantation.

What Are the Strategies to Prevent SFSS in Steatotic Patients?

The impact of fat deposits in the liver in enhancing SFSS after major liver surgery and partial OLT has been discussed above. Taken together, although assessment of hepatic steatosis and its associated risk are difficult,⁵⁹ the protective strategy by Ω -3 fatty acid supplementation has been demonstrated in several animal models. Mechanistically, Ω -3 fatty acids ameliorate the ischemic injury of the steatotic mouse liver via partial resolution of steatosis, improvement of the microcirculation,⁶⁰ and its strong anti-inflammatory properties,

which is also active in lean animals.⁶¹ Ω -3 fatty acids act also through eicosanoid derivatives, which counteract the proinflammatory Ω -6 eicosanoids.⁵⁴ It has been shown that oral administration of Ω -3 fatty acids to patients with liver steatosis significantly improves the fatty echotexture.⁶² As presented above (Fig. 3), we have successfully treated three candidates for living donation with Ω -3 fatty acids. It was also shown that intravenous Ω -3 fatty acids prevent liver injury in children receiving total parenteral nutrition.¹³³

Conclusion

In summary, SFSS is one of the most challenging complications following major liver surgery and partial OLT. A large effort to better understand the underlying mechanisms and identified protective strategies is warranted, because solving SFSS would enable safer partial OLT with splitting of cadaveric grafts for two adults or safer living donor hepatectomy, thereby making grafts available for many more recipients. Similarly, curative liver resection could be offered to more patients with multiple and otherwise nonresectable tumors. The only well-established and effective strategies are portal vein occlusion to induce regeneration of the contralateral side, or the so-called "two stage" procedure for major liver surgery. Novel approaches include targeting specific pathways such as nitric oxide with sevoflurane, and IL-6 with PTX or cardiotrophin. Finally, the use of Ω -3 fatty acids may prevent injuries related to steatosis. It is likely that the many groups working in this field will provide new directions in the search for an effective strategy to prevent and cure SFSS.

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