23- The ‘small for size’ liver syndrome (SFSS)

- **Definition:** a clinical syndrome, which occurs in the presence of a reduced mass of liver insufficient to maintain normal liver function.
- The syndrome is characterized by postoperative liver dysfunction with prolonged cholestasis and coagulopathy, portal hypertension, and if severe with ascites.
- The continuing liver dysfunction predisposes to further complications including sepsis, and gastrointestinal bleeding.
- Significantly higher rates of hemorrhage and intestinal perforation requiring relaparotomy and lower graft survival are reported.
- These features can persist for several weeks, with improvement if the liver recovers satisfactorily.
- The biochemical profile includes cholestasis with elevated conjugated bilirubin, mild to moderate elevation of transaminases, and prolonged prothrombin time.
- Histological features include cholestasis with bile plugs, and areas of regeneration and ischemia with patchy necrosis.
- In the context of liver transplantation (LT), approximately 50% of recipients with SFSS will die of

**Assessment of liver volume**

<table>
<thead>
<tr>
<th>Nomenclature for liver volumes</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLV Total liver volume</td>
</tr>
<tr>
<td>SLV Standardised liver volume</td>
</tr>
<tr>
<td>FRL Future remnant liver</td>
</tr>
<tr>
<td>SFLR Standardised future liver remnant</td>
</tr>
<tr>
<td>FL Functional liver</td>
</tr>
<tr>
<td>ERFL Estimated rate of functional future remnant liver</td>
</tr>
<tr>
<td>GRBWR Graft-to-recipient body weight ratio</td>
</tr>
<tr>
<td>GWR Graft weight ratio</td>
</tr>
<tr>
<td>VR Volume ratio</td>
</tr>
</tbody>
</table>

- In the past, preoperative assessment concentrated on the volume of liver to be removed.
- Currently, efforts are directed towards an accurate definition of the minimum liver volume (LV) needed to achieve satisfactory recipient survival following transplantation, or patient survival following resection.
- There is a lack of consensus on the volume of liver that can be safely resected, due to a lack of standardization in preoperative volumetric assessment, with publication of several formulae, varied nomenclature, and disparity between Western and Eastern populations.
- A number of formulae are described; Total LV (TLV), graft volume, and functional remnant liver (FRL) can be accurately measured by three-dimensional CT volume reconstruction on the basis of BSA and body weight. Measurement of volume ratios correlate with the etiology and severity of chronic liver disease (CLD), and are reliable predictors for patient survival.
• However, formulae based on BSA and patient weight underestimate TLV in Western compared with Japanese individuals. Importantly, TLV in an average Western adult can be 15% greater than a Japanese adult for the same BSA.
• Traditional techniques to measure the LV to be resected prior to hepatectomy can lead to inaccurate estimates of total tumor and FRL volumes.
• Problems may arise because of the presence of dilated bile ducts, multiple tumors, undetected lesions, compromised liver volume due to cholestasis or previous chemotherapy, cholangitis, vascular obstruction, steatosis or cirrhosis, or segmental atrophy and/or hypertrophy from tumor growth.
• Accurate preoperative assessment by CT volumetry is necessary as significant interpatient variation exists in hepatic volumes.
• In most patients the right LV represents >50% of TLV (median, 65% of TLV), with a range of 45-80% of TLV.
• The contribution of the left liver to the TLV is also variable with a range of 15-45% of TLV. The left liver contributes <=25% of TLV in >10%.
• In LDLT, CT measured TLV and FRL can be used to predict postresection function as the donor liver is normal.
• However, the TLV of the recipient’s diseased liver is not a useful index of function.
• Values calculated from graft weight-to-recipient body weight ratio (GRBWR), or standardized liver volume (SLV) based on recipient BSA are used to predict minimum adequate graft volume.
• In split liver transplantation (SLT) and LDLT, a GRBWR of >=0.8% or a graft weight ratio (graft weight divided by standard liver weight of recipient) of >=30% are recommended to achieve graft and patient survival of >90%.
• In the presence of steatosis, particularly >30%, graft weight alone is not a suitable guide.
• In comparison, extended resection of 80% of functional parenchyma can be performed in the absence of chronic liver disease for hepatobiliary malignancies.
• Recommended minimal functional remnant LV following extended hepatectomy is >=25% in a normal liver, and >=40% in an ‘injured’ liver, with moderate to severe steatosis, cholestasis, fibrosis, cirrhosis, or following chemotherapy.
• CT volumetry measured LVs are unreliable in patients with CLD. Other predictors of outcome should be assessed such as grade of fibrosis, age, hepatocellular injury, Child-Pugh classification, and in particular the presence of portal hypertension.
**SFSS following extended heptatectomy**

- The percentage of remaining liver is more specific in predicting hepatic dysfunction than the anatomic extent of resection
- Risk assessment for major heptatectomy is dominated by accurate preoperative prediction of postresection hepatic dysfunction.
- Evaluation of liver biochemistry, Child-Pugh classification, and indocyanine green clearance (ICG) measure total liver function.
- When compared with ICG and CT volumetric data, hepatobiliary scintigraphy is a reproducible accurate tool to assess functional liver uptake and excretion, preoperative liver function reserve and remnant liver function, and allows monitoring of postoperative liver function regeneration
- Methods to assess liver function before and in the early period after resection include estimation of biliary bile acid, hepatocyte growth factor and interleukin-6 concentrations
- Caution is advised when planning major resections in patients with fatty livers. A recent study demonstrated a higher rate of total and infective complications in patients with >30% steatosis following >=1 lobe hepatic resection with a nonsignificant trend toward higher 60-day mortality
- Assessment of future remnant volume distinguishes those who will most likely benefit from preoperative liver enhancement techniques with portal vein (PVE) or hepatic artery embolisation.
- The selective use of embolisation techniques increases tolerance to major hepatic resection by reducing the liver volume requiring resection, and inducing hypertrophy of the FLR to approximate target limits in patients with large tumors or abnormal liver function.
- Criteria for selection of patients for PVE prior to major heptatectomy are FLR size, factors compromising liver function including previous chemotherapy, hepatitis and cirrhosis, and the planned complexity of the procedure
- It is recommended when predicted FLR is <=20-25% in a normal liver, and <=40% in a liver with compromised function.
- PVE results in increased volume and function of the FRL, with documented increased biliary excretion and decreased postoperative hepatic dysfunction.
- It allows patients with previously unresectable disease to benefit from resection with comparable long-term survival
- The factors influencing the effect of PVE are unclear.
- Significantly elevated levels of serum transforming growth factor-[alpha] (TGF-[alpha]) associated with hypertrophy of the non-embolised lobe. Measurement of serum TGF-[alpha] may assist in planning optimal time of subsequent heptatectomy. Serum hyaluronic acid <=100 mg/L and procollagen type III peptide <=0.7/ml have been used to identify patients with active hepatitis or cirrhosis who may benefit from PVE before right heptatectomy
- In hepatocellular carcinoma, (99 m) Tc-galactosyl human serum albumin scintigraphy before and 2 weeks after PVE allowed selection of patients suitable to progress to resection.
SFSS following liver transplantation

- Due to an increasing scarcity of donor organs there has been continuing surgical innovation to try to improve graft availability, including the use of the techniques of liver splitting and LDLT.
- For the right lobe graft, good risk recipients who are stable, well nourished with mild-to-moderate portal hypertension, a GRBWR of 1% should be sufficient to avoid SFSS.
- For decompensated patients, particularly those with severe portal hypertension, the GRBWR should be >=1.5%.
- There are several advantages to LDLT including that it is possible to preoperatively predict graft function.
- Posttransplant liver dysfunction can occur when a functionally SFS whole graft is used:
  1. Donors with abnormal liver function tests particularly elevated serum bilirubin and gamma glutamyl transferase, prolonged cardiac and/or respiratory arrest,
  2. Administration of high dosage of vasopressors,
  3. Severe systemic sepsis,
  4. Steatosis,
  5. Prolonged ICU stay >5 days,
  6. Hypernatraemia, and
  7. Non-heart beating donors with
  8. Prolonged ischaemic times.
  9. Steatosis >30%.
- Fatty infiltration of 30% or more should preclude using a liver for splitting or auxiliary grafting because of the inability to predict subsequent function and the increased likelihood of SFSS.
- Donor age >50 years is associated with reduced regenerative capacity, increased susceptibility to prolonged cold ischemia, increased rates of early graft dysfunction and prolonged cholestasis.
- The status of the recipient is also an important variable.
- Recipient factors that predict poor outcome and SFSS include,
  1. poor metabolic and physical condition,
  2. advanced CLD and
  3. severe portal hypertension,
  4. impaired venous inflow and/or outflow.
- Probably the most important factor is portal hypertension, and recipients with advanced CLD need larger and better functioning grafts to avoid SFSS.

Pathophysiology

1. Inadequate functional liver mass,
2. excessive portal perfusion and
3. exposure to gut-derived endotoxin
are implicated in the pathophysiology of SFSS.
- After major hepatectomy, the residual liver increases rapidly in size over the first 2 postoperative weeks.
It has been difficult to separate out true regeneration from hypertrophy in this setting.

The extent of liver resection, BSA, combined portal vein resection and preoperative PVE are significantly associated with the rate of restoration of liver size within this period.

Major hepatectomy results in parenchymal loss, and a reduced intrahepatic vascular bed with higher portal flow per gram of remnant liver and increased portal pressure.

During liver regeneration functional recovery may be hindered by increased hepatic portal resistance due to transient sinusoidal narrowing.

The increase in portal pressure and mesenteric flow causes sinusoidal endothelial and Kupffer cell injury with release of inflammatory cytokines.

In LT, excessive portal flow with portal hypertension after reperfusion is postulated to lead to direct and indirect graft injury due to hemodynamic interactions between portal vein and hepatic artery flow.

Following reperfusion of SFS grafts at SLT, portal vein flow (PVF) is inversely related to graft size, while hepatic artery flow is reduced proportionately to graft size.

After right lobe LDLT, portal peak systolic velocity at postoperative day 1 is increased to 30 cm/s in recipients of cadaveric whole organs, 50 cm/s and 115 cm/s in recipients of organs with GWBWR >1.2%, and GWBWR <0.9%

Also, increased recipient serum total bilirubin on postoperative day 2 correlates with higher recipient portal flow one hour after reperfusion.

Impaired hepatic arterial flow in SFS grafts following LDLT appears to be related to increased PVF [ ]

In right lobe LDLT SFS grafts of <40% of standard liver weight, transient portal hypertension has been documented early after reperfusion associated with ultrastructural evidence of sinusoidal damage, intragraft endothelin-1 up-regulation with down-regulation of heme oxygenase-1 and heat shock protein 70, and reduced level of plasma nitric oxide.

Irreversible endothelial cell injury in SFS grafts after reperfusion resulting in microcirculatory failure may play a role.

Management

Prior to major hepatectomy, ischemic preconditioning of the liver has been successfully employed to protect against subsequent prolonged periods of ischemia.

This strategy may also be of benefit in LT to protect SFS grafts, as it has been shown to maintain the hepatic microcirculation and decrease Kupffer cell activation.

Avoidance of warm ischemia, a short cold ischemic time, and early treatment of rejection are important elements in optimizing SFS graft function.
The 'small for size' liver syndrome

- Perfusion of the remnant liver after hepatectomy or graft after LT is important.
- Impaired venous inflow and/or outflow may significantly reduce hepatic function.
- In right lobe LDLT without the MHV, reconstruction of drainage veins from the anterior segment is indicated with a potentially SFS graft.
- Interposition grafts using donor iliac artery or vein, or recipient inferior mesenteric, ovarian or saphenous veins have been used.
- Reconstruction of accessory hepatic veins in right lobe LDLT is recommended if >=10mm diameter to maximize venous outflow and indirectly liver perfusion.
- In LDLT, a right lobe graft with retention of the MHV is physiologically superior. A recent study has demonstrated the safety of right lobe LDLT grafts with MHV retention; however, the risk to the donor is increased.
- After liver resection care must be given to ensuring the remnant liver is well perfused.
- Liver fixation will ensure that venous outflow obstruction/impairment does not occur and compromise function.
- The importance of portal hypertension in determining the fate of SFS grafts has led to the development of techniques of venous inflow modification.
- Poor graft outcome has been reported in SFS grafts with PVF >260 ml/min/100 g graft and elevated portal vein pressure.
- Portal venous inflow has been reduced in a number of ways. The diversion of superior mesenteric flow by a meso-caval shunt with downstream ligation of the superior mesenteric vein was reported after adult LDLT with SFS grafts.
- The addition of porto-mesenteric disconnection in animal studies with GRBWR of 0.6% was effective in improving survival.
- Another technique is splenic artery ligation (SAL) with or without splenectomy, which maintains hepatic artery inflow and prevents the effects of secondary hypersplenism.
- If there is an insufficient response to SAL, then graded porto-caval shunt, portal vein band, or porto-mesenteric disconnection should be considered
- Pharmacological perioperative protection of the liver, liver support with liver-assist devices and hepatocytes, and perioperative enhancement of liver regeneration will undoubtedly improve outcome

References:
1. O. N. Tucker and N. Heaton The ‘small for size’ liver syndrome, Current Opinion in Critical Care 2005, 11:150—155