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Literature Review

Small-for-size syndrome in adult liver transplantation: A review

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ABSTRACT

Small-for-size syndrome remains the greatest limiting factor for the expansion of liver transplantation (apart from cadaveric organ donation) and has been the major cause of worse short-term prognoses after LDLT. The size of the graft, (GRWR < 0.8 or graft to SLV ratio <30–40%, portal hyperperfusion, obstructed hepatic venous drainage, MELD score, and graft steatosis may be responsible for the pathogenesis of SFSS. Sinusoidal shear stress may be the principal common pathway in the pathogenesis. Living donor grafts with portal pressure more than 20 mmHg or portal flow exceeding 250 mL/min per 100 g have a higher risk of graft failure. The role of decrease arterial flow in response to portal hyperflow remains to be elucidated. Acute portal hypertension and increased shear stress caused by a partial hepatectomy triggers the regeneration of the remaining liver, though liver dysfunction is seen to be due to sudden portal hypertension, microcirculatory ischemia, reduced oxygen delivery, and hepatocellular dysfunction. The differences in sinusoidal pressure, or differences in the hepatotropic substances delivered to the graft or the liver remnant may be the difference between grafts that survive and grafts that don't. We need to find the threshold level of hyperperfusion that does more harm than good.

1. Introduction and background

Since the 1990s, surgical advances have made it possible to use partial liver grafts arising from a living donor or a split cadaveric liver, and their use constitutes an important strategy for increasing the number of organs. The use of partial grafts, however, may be associated with small-for-size syndrome (SFSS). The concept of small-for-size (SFS) liver grafts used in patients undergoing living donor liver transplantation (LDLT) was first reported in 1999.[1] Liver grafts with a graft/standard liver volume ratio less than 0.4 or a graft/recipient weight ratio (GRWR) less than 0.8% were considered small-for-size grafts, resulting in prolonged cholestasis, ascites, coagulopathy, and encephalopathy. This clinical scenario secondary to SFS grafts was described as small-for-size syndrome (SFSS).[2]

Small-for-size syndrome after right lobe liver transplantation (AALRLT) still remains the greatest limiting factor for the expansion of using segmental liver transplantation and the major cause of worse short-term prognoses after LDLT. After more than a decade of this entity being described the causes of SFSS are still not clear.

2. Pathogenesis

Patients undergoing liver transplantation usually have portal hypertension and therefore are likely to have a high portal

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blood flow in the transplanted graft. The graft volume in adult living donor liver transplantation with partial liver transplantation is usually approximately 60–65% of the donor liver, and various problems that may affect the prognosis often occur because the partial graft cannot sustain excessive portal blood perfusion. Hence, liver transplant recipients can potentially develop a specific syndrome known as "small-for-size syndrome", when a small-for-size graft causes size mismatch in the presence of portal hypertension. We saw similar findings in a patient who underwent revascularization for chronic mesenteric ischemia, and developed clinical manifestations similar to PHP or portal hyperperfusion. This clinical development may be due to the sinusoidal stress injury that has been described in literature.

SFSS is thought to be attributable to a graft that is probably too small to meet the demands of a transplant recipient. Other factors not related to the size of the graft, such as a GRWR (graft to recipient body weight ratio) $< 0.8\%$ and a graft to standard liver volume ratio (G/SLV) $< 30\%$–40%, but also portal hyperperfusion (excessive venous inflow), obstructed hepatic venous drainage, the clinical condition of the recipient (MELD score), and graft steatosis may all be responsible for the pathogenesis.[3] Portal venous inflow resulting in sinusoidal shear stress in particular is thought to be a primary factor involved in the development of SFSS and failure of a partial liver graft. The reduction in the intra-hepatic vascular bed results in higher portal flow per gram of liver tissue, a rise in portal pressure, and stress in the hepatic sinusoid.[4–6] This sinusoidal shear stress may cause sinusoidal endothelial cell injury, which leads to subsequent processes of hepatocellular damage and death.[7,8]

However, though SFSS develops from smaller grafts, the actual circumstances that predispose recipients of liver transplants to this process remain elusive. The histopathology of the engrafted liver in SFSS is characterized by hepatocyte ballooning, steatosis, centri-lobular necrosis, and parenchymal cholestasis.[9] The resulting high portal flow causing portal hypertension results in irreversible sinusoidal damage with endothelial injury and structural damage in rats[10] (Figs. 1 and 3). This damage has also been demonstrated by electron microscopy in human SFSS grafts[11] (Fig. 2).

Hyperdynamic portal flow through a small liver graft leads to shear stress injury to hepatic sinusoidal endothelial cells.[12] With the loss of integrity of endothelial cells, leukocytes adhere to the sub endothelial hepatocytes and initiate the coagulation cascade and inflammatory cascade within the damaged sinusoids causing impaired blood flow. Subsequently there is upregulation of vasoconstrictive genes, like endothelin-1 and early growth response-1 (EGF-1 [endothelial growth factor]). This sets of the cascade coordinating upregulation of divergent gene families related to ischemia-reperfusion injury.[14,15]

During the early period (within 24 h) after reperfusion, local tissue macrophages, mainly Kupffer cells initiate portal tract infiltration, followed by circulating inflammatory cells. Reactive oxygen radicals are released from infiltrating macrophages, leading to more liver damage.[13,16] Increased vascular endothelial growth factor (VEGF) secreted during rapid liver regeneration and angiogenesis contributes to portal tract infiltration. VEGF induces Flk-1-dependent macrophage migration and activation in the liver graft.[17] Therefore, there is enhanced alloantigen presentation which could lead to acute rejection.[18,19]

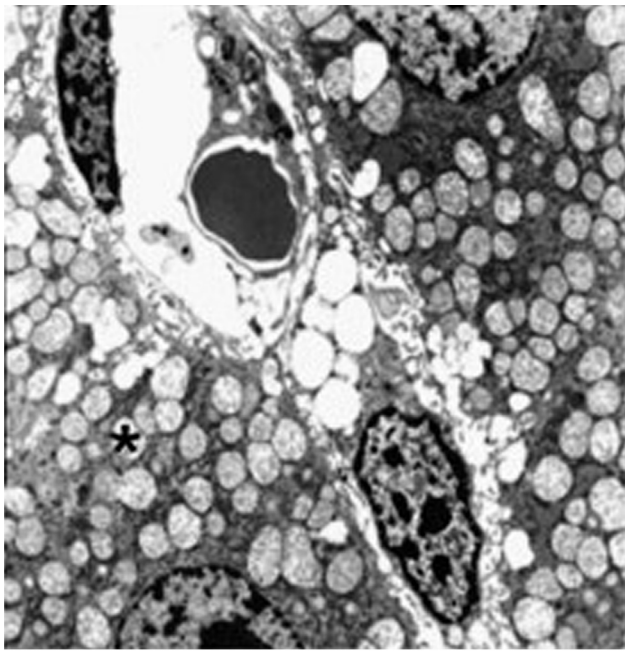

Fig. 1 – EM picture of SFSS in a rat model showing mitochondrial swelling (asterisk); and endothelial disruption at 1 h after reperfusion.

Thus, small-for size graft injury could be viewed as a combination of mechanical injury, exacerbated inflammatory response,[13] and subsequent accelerated immune reaction on top of ischemia-reperfusion injury.

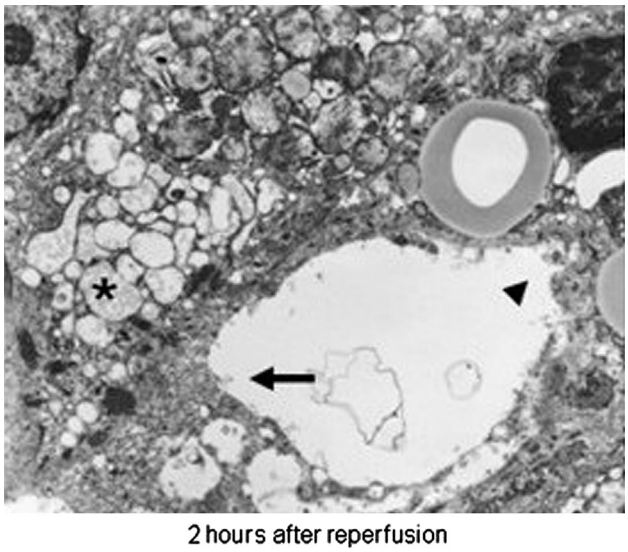

Fig. 2 – Ultrastructure human SFSS; mitochondrial swelling (asterisk), loss of microvilli in space of Disse (arrow), and gaps between endothelial cells (arrowhead).