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Title: Small-for-size syndrome in living-donor liver transplantation

Running Title: SFSS in LDLT

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Abstract

When the graft volume is too small to satisfy the recipient's metabolic demand ("small-for-size graft": SFSG), the recipient may thus experience "small-for-size syndrome" (SFSS). Because the occurrence of SFSS is determined by not only the liver graft volume but also a combination of multiple negative factors, the definitions of SFSG and SFSS are different in each institute and at each time.

In the clinical setting, surgical inflow modulation and maximizing the graft outflow are keys to overcoming SFSS. Accordingly, relatively smaller-sized grafts can be used with surgical modification and pharmacological manipulation targeting portal circulation and liver graft quality. Therefore, the focus of the SFSG issue is now shifting from how to obtain a larger graft from the living donor to how to manage the use of a smaller graft to save the recipient, considering donor safety to be a priority.

Introduction

In the last 20 years, the indications for living-donor liver transplantation (LDLT) have been successfully expanded from pediatric to adult cases. However, the use of grafts smaller than the native liver is unavoidable in cases of LDLT performed on adults. When the graft volume is too small to satisfy the recipient's metabolic demand ("small-for-size graft": SFSG), the recipient may thus experience "small-for-size syndrome" (SFSS). "SFSS" is characterized clinically by a combination of prolonged functional cholestasis, intractable ascites, and delayed functional recovery of both prothrombin time and encephalopathy (1-3). To avoid SFSG, the use of a larger-sized graft, such as the right lobe graft, is the standard strategy for adult-to-adult LDLT (4-7). However, although a right-lobe LDLT can provide an adequate graft size to meet the metabolic demands of most adult recipients, "SFSS" can be observed not only in "SFSG" recipients but also in larger-sized graft recipients (8-10). Therefore, the occurrence of SFSS is determined by not only the liver graft volume but also a combination of multiple negative factors.

However, the procurement of a liver graft of greater volume imposes a greater risk on the donor because the remaining portion of the liver in the donor is smaller. Accordingly, the

criteria for SFSG in adult-to-adult LDLT have been revised recently at several institutes

(2, 11). In other words, a relatively smaller-sized graft, such as the left lobe, can be used in

adults with surgical manipulations aimed at reducing the portal venous pressure (PVP)

and flow (PVF) (11, 12). Therefore, the focus of the SFSG issue is now shifting from how

to obtain a larger graft from the living donor to how to manage the use of a smaller graft to

save the recipient, considering donor safety to be a priority.

Definition

Kiuchi et al. (1) defined "SFSG" as a < 0.8% graft-to-recipient body weight ratio

(GRWR). They reported that the use of "SFSG" leads to "SFSS," including poor bile

production, delayed synthetic function, prolonged cholestasis and intractable ascites, with

subsequent septic complications and higher mortality. Sugawara et al. (13) suggested that

a graft volume/standard liver volume ratio (GV/SLV) < 40% was associated with

decreased survival and the prolonged recovery of liver function. At present, some

institutes have established criteria for graft selection with a lower GRWR than before:

GRWR > 0.8% (14, 15) or GRWR > 0.6% in combination with PVP control (11); these

criteria show that the definition of "SFSG" has become lower in LDLT. Although there

has been no accepted definition of "SFSS" until now, several different definitions for

SFSS or liver graft dysfunction have been given (3, 16-18) (Table 1).

Pathophysiology

I.   Relative shortage of vital liver volume for life maintenance

The first possibility of the pathogenesis of poor prognosis in SFSG is the relative shortage

of hepatic parenchymal cells. Previous clinical analyses have suggested that a normal

liver can tolerate a partial hepatectomy to 25 - 27 % of the residual volume (19-21).

II.   Portal hypertension: shear stress

The characteristic microscopic findings of SFSS, including hepatocyte ballooning and

cholestasis, are thought to be due to microcirculatory disturbances (22). Many

experimental and clinical studies (12, 23-28) suggest that elevated PVP (shear stress)

forms the central pathogenesis of SFSS. A persistent elevation of the PVP in the graft,

which is attributable to hyperdynamic splanchnic circulation (29) and limited

accommodation of the graft, causes sinusoidal endothelial cell injury (25) and the release

of deleterious mediators (30), which ultimately lead to serious graft injury. Shear stress

also leads to an imbalance in the expression of intragraft vasoregulatory genes, such as

endothelin-1 and nitric oxide (31). Microcirculatory disorders in SFSG will eventually

result in graft dysfunction (32).

III. Arterial hypoperfusion

The role of arterial hypoperfusion in SFSS is less well studied as it is secondary to portal

hyperperfusion. Low hepatic artery flow is considered to be due to a homeostatic

mechanism known as the hepatic arterial buffer response (33). In states of extreme portal

hyperperfusion, such as those observed in SFSG, an exaggerated hepatic arterial buffer

response may contribute to ischemic injury, ischemic cholangitis, and cholestasis.

IV. Intestinal mucosal injury

We demonstrated that the intestinal mucosa was severely damaged with portal

hypertension following SFSG liver transplantation in swine (26). Several experimental

studies (34-39) have revealed that portal hypertension in liver cirrhosis can increase

bacterial translocation by inducing congestion and edema of the intestine. Accordingly,

bacterial translocation could be developed in an SFSG-transplanted recipient due to the

elevation of mucosal permeability, which is compatible with the clinical aspect of a

higher postoperative infection rate in SFSS (40).

*V.	Liver regeneration*

After extensive hepatectomy or segmental liver transplantation with an SFSG, liver

regeneration is essential for patient survival. Liver regeneration is a highly complex and

organized process that has been shown to involve the actions of a number of cytokines

and growth factors, such as hepatocyte growth factor (HGF) (41), transforming growth

factor-α (42), epidermal growth factor (43), hepatocyte growth factor activator (HGFA)

(44) and vascular endothelial growth factor (VEGF) (45). Shear stress is well defined as a

putative trigger mechanism for liver regeneration (46-48). During the first week after a

partial liver transplantation, the partial liver graft regenerates quickly, up to

approximately 80-100% compared with the standard liver volume (47). Ninomiya et al.

(49) showed that SFSGs regenerated faster and were associated with significantly higher

peripheral HGF levels one day after LDLT than non-SFSGs. Many previous studies have

suggested that the elevation of PVF or shear stress induces liver regeneration and that

insufficient PVF induces hepatic atrophy and liver failure (50-57). Portal hyperperfusion

can promote liver regeneration only if it is limited to a certain extent. Hessheimer et al.

(58) suggested that the liver graft requires PVF superior to its normal baseline value for liver regeneration and that a calibrated portocaval shunt (PCS) that maintains the PVF at twice its baseline value produces a favorable outcome after swine liver transplantation with a 30% SFSG.

Clinical Factors influencing SFSS

I. Quality of the graft

Factors regulating liver graft compliance would be the potential definition of the graft quality, such as donor age, steatosis, and ischemic injury. Other unknown factors may also precipitate SFSS.

a. Ischemic injury

Both warm (59) and cold ischemia (60) have been shown to impair regeneration after partial liver transplantation. The difference in the essential liver volume after the operation between an extended hepatectomy and partial liver transplantation may owe much to the existence of this issue.

b. Steatosis

A steatotic liver graft from a deceased donor with a longer cold ischemic time is well known to be associated with poor graft function and survival. A previous study revealed that steatotic liver grafts are related to the increased susceptibility to ischemia-reperfusion injury (61, 62), including impaired graft microcirculation and PVF, increased hepatocellular damage observed serologically and histologically, increased pro-inflammatory cytokine production, and decreased ATP concentration. However, in an LDLT setting with a shorter cold ischemic time compared with a deceased donor graft, Hayashi et al. (63) reported that early graft function after LDLT was similar in mild and moderate steatosis but that severe steatosis was significantly associated with poor graft function and survival. In any case, SFSS is determined by a combination of multiple negative factors, and steatotic liver grafts should be avoided if the graft volume is small.

c. Donor age

Moon et al. (64) have shown that an older donor age affects graft prognosis only when combined with an SFSG. Ikegami et al. (65) reported that the function and regeneration of the allografts from older donors in LDLT are worse than those of their younger counterparts. Tanemura et al. also (66) reported that donor age ($\geq$ 50 years) was

independently correlated with impaired remnant liver regeneration at 6 months in right

lobe LDLT.

d. Congestion

The magnitude of the impact of tissue congestion caused by interrupted venous drainage

is highly variable among grafts. Severe congestion in the anterior segment has been

reported to occur in right lobe grafts without the middle hepatic vein, which leads to

massive ascites and graft dysfunction (8).

II. Perioperative recipient related factors

A. Preoperative recipient status:

With respect to the maintenance of the initial graft function, the post-transplant metabolic

and synthetic demands in recipients with severely damaged liver function

(hyperbilirubinemia, coagulopathy) and a pre-operative deteriorated general condition

(renal dysfunction, septic state, etc.) aggravate the metabolic function of the graft (1, 67).

Furthermore, the liver grafts may be insufficiently functional for the excessive metabolic

and synthetic demands of high-risk recipients, including their reduced metabolic and

synthetic capacities. Therefore, a pre-operative deteriorated condition with a high model

for endstage liver disease (MELD) score may impair the function of the graft, leading to graft dysfunction, graft failure and eventually multiple organ failure, especially in SFSG. Yoshizumi et al. (68) reported that a larger graft is necessary if the donor age is > 50 years and the MELD score is >20. Accordingly, Ikegami et al. (69) recommended that high-risk patients should receive a larger, younger graft to minimize the risk of SFSS.

B. Portal circulation (Pressure and Flow):

After LDLT, Ogura et al. (70) demonstrated that a PVP <15 mmHg is associated with good patient outcome in a retrospective clinical analysis: patients with a PVP <15 mmHg demonstrated a better 2-year survival (93.0%) than patients with a portal pressure ≥15 mmHg (66.3%).

Hessheimer et al. (58) reported that the PV-inferior vena cava (IVC) pressure gradient and PVP were significantly higher in SFSG liver transplantation in swine and that the PCS decreased both the PVP and PV-IVC pressure gradients. However, Ogura et al. (12) reported in a retrospective clinical study of LDLT that although the PV-IVC pressure gradient was higher in the group with the higher PVP, there were no significant differences in the 1- and 3-year survival rates when they divided and analyzed their study

group by low (< 9 mm Hg) and high (≥ 9 mm Hg) PV-IVC pressure gradients. Further experiments or clinical trials of SFSG are necessary to determine whether the PVP or PV-IVC pressure gradient is more significant for SFSG.

In clinical research, we showed that a high compliance (PVF/PVP) graft in which the PVF can be maintained at a high level despite a low PVP is a good graft for postoperative liver graft function (71). The optimal portal venous circulation for the liver graft could depend on the graft size and quality.

Intervention to avoid SFSS

(1) Graft selection: increase the graft volume and maximize the outflow

After the concept of "SFSS" had been reported, the graft type shifted from the left side to the right side of the liver to increase the liver graft volume. Dual graft liver transplantation was also proposed when two donors were available in some institutes (72, 73).

Regarding the usage of a "right-side graft", to avoid the development of a congested area in the anterior segment, some institutes have preferred to use a "with MHV graft". Fan et al. chose an extended right-lobe graft with the MHV (74). In contrast, the additional

venous reconstruction of the anterior segment with an interposition vein graft has been

adopted by Lee et al. (8). The reconstruction of the segment V and VIII branches using

jump grafts has been reported (75). In our institute, we have performed the venous

reconstruction of the anterior segment together with an anterior patch plasty of the hepatic

vein using the native portal vein to maximize the liver graft outflow (76).

We reported that the compliance per unit of graft weight in left-lobe grafts is higher than

in right lobe grafts without MHV in LDLT (71). Shimada et al. (77) also reported that

left-lobe grafts are a feasible option for LDLT because the outflow of the left-lobe graft is

considered superior to that of the right-lobe graft and in the case of right-lobe grafts

without the MHV, hepatic venous drainage is one of the most critical problems.

Accordingly, beginning in December 2007, our institution has actively selected the

left-lobe graft for use in LDLT to maximize the graft outflow and minimize the risks to

the healthy donor.

(2) Portal inflow modulation

Boilot et al. (78) first reported a case in which a recipient-transplanted SFSG with a

GRWR of 0.61% was successfully treated by the reduction of PVP with a mesocaval

shunt. Thereafter, several surgeons have reported the successful treatment of SFSG by

surgical manipulations to reduce the PVP and PVF with a splenic arterial ligation (28),

PCS (27, 79, 80) or splenectomy (12, 81-83) in clinical and animal studies (84, 85).

However, because the diversion of portal inflow can lead to liver necrosis or atrophy, an

adequate PVF is essential for liver regeneration (26, 52, 58). We reported that an

SFSG-transplanted swine with a large PCS could not survive more than 5 days after liver

transplantation, with its autopsy showing massive hepatic necrosis. A large PCS, which

would greatly reduce the PVF and therefore result in graft failure, should be avoided (26).

Therefore, in our institution, a splenectomy is performed first to decrease the PVP (< 15

mmHg), and all large collaterals are ligated to prevent the steal phenomenon in some

situations, which decrease the compliance after LDLT (such as rejection) (83).

(3) Other interventions

In experimental research, several pharmacological interventions have been reported to

improve the survival after SFSG, including the portal infusion of prostaglandin E1 (86),

granulocyte colony-stimulating factor (87), endothelin A receptor antagonist (31), redox

factor-1 (88), somatostatin (89), and hyperbaric oxygen treatment (90) to promote liver

regeneration or reduce ischemia-reperfusion injury after an SFSG liver transplantation.

(4) Organ preservation

Newly developed preservation solutions, such as POLYSOL (32), activated protein C

(91) in preservation solution, and cold preservation using retrograde nitric oxide with

oxygen administration, for SFSG liver transplantation (92) were reported to recondition

the liver graft viability and promote liver regeneration in rats.

Conclusion

SFSG has become an issue again with respect to pursuing donor safety. Because the

occurrence of SFSS is determined by not only the liver graft volume but also a

combination of multiple negative factors, we should manage all risk factors and make

efforts to improve the outcomes associated with SFSG.

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Table 1: Proposed definitions of small-for-size syndrome

	Definition
Dahm et al. [3], 2005	**Small-for-size dysfunction (SFSD)** Dysfunction[*] of a 'small' partial liver graft (GRWR < 0.8%) during the first postoperative week after the exclusion of other causes[***]. **Small-for-size non-function (SFSNF)** Failure[**] of a 'small' partial liver graft (GRWR < 0.8%) during the first postoperative week after the exclusion of other causes[***].
Soejima et al. [16], 2006	**Small for size syndrome** Prolonged cholestatis (T.Bil >10 mg/dL on POD14) and intractable ascites (ascites > 1 L on POD 14 or >0.5 L on POD 28).
Hill et al. [17], 2009	**Small for size syndrome** T.Bil >10 mg/dL (and continuing to increase) after POD 7, PT-INR >1.5 and ascites >2 L, excluding mechanical/technical problems.
Ikegami et al. [18], 2012	**Delayed functional hyperbilirubinemia (DFH)** with T.Bil >20 mg/dL For >seven consecutive days after POD 7, excluding technical, immunological and hepatitis factors.

[*] Graft dysfunction = the presence of two of the following on three consecutive days:

bilirubin >100 lmol/l, INR > 2, encephalopathy grade 3 or 4.

[**] Graft failure = re-transplantation or death of recipient.

[***] Exclusion criteria: technical (e.g. arterial or portal occlusion, outflow congestion,

bile leak), immunological (e.g. rejection), infectious (e.g. cholangitis, sepsis).