more accurate estimation of liver fibrosis compared with currently used measures before hepatectomy for hepatobiliary surgeons.

Terminology

^{99m}Tc-GSA liver scintigraphy: Technetium-99m-diethylenetriaminepenta-acetic acid-galactosyl human serum albumin liver scintigraphy. SPECT analysis: Single-photon emission computed tomography analysis.

Peer review

The manuscript evaluates the utility of ^{99m}Tc-GSA SPECT to reliably predict the degree of liver fibrosis in patients for liver resection is planned. Comparisons are made to particularly state that hepatic clearance is superior to other measurements (LHL15 and HH15), other techniques (ICGR15), and clinical parameters of liver function when predicting fibrosis. The study has relevance and is interesting in its concept; however some conclusions are made that need to be justified by more rigorous data analysis.

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ELSEVIER

Establishment of Educational Program for Multiorgan Procurement From Deceased Donors

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ABSTRACT

Introduction. Multiorgan procurement is not an easy procedure and requires special technique and training. Since sufficient donors are not available for on-site training in Japan, establishment of the educational program for multiorgan procurement is mandatory.

Materials and methods. Development of e-learning and simulation using pigs are our main goals. E-learning contains three dimensional computer graphic (3DCG) animations of the multiorgan procurement, explanation of both donor criteria and procurement procedure, and self-assessment examination. To clarify the donor criteria, the risk factors to 3-month survival of the recipients were analyzed in 138 adult cases of liver transplantation. The 3DCG animation for liver procurement was developed, which was used in the lecture prior to the simulation on August 10, 2013. The results of the examination after this lecture (exam 2013) were compared with the results after the lecture without using animation in 2012 (exam 2012). The simulation was performed by 97 trainees divided into 9 teams, and the surveys were conducted.

Results. The risk factors for early outcome of the recipients were cold ischemia time ($\geq$10 hours), Model for End-stage Liver Disease score ($\geq$20), and donor age ($\geq$55 years). Results of examination showed that overall percentage of the correct answers was significantly higher in exam 2013 than in exam 2012 (48.3% vs 32.7%; $P = .0001$). The survey after the simulation of multiorgan procurement revealed that most trainees thought that the simulation was useful and should be continued.

Conclusion. The novel educational program could allow young surgeons to make precise assessments and perform the exact procedure in the multiorgan procurement.

ALTHOUGH the number of deceased donors slightly increased since 2010 when the organ transplantation law was revised, there is still a large mismatch between supply and demand of deceased donors in Japan. To maximize the organ utility, multiorgan procurement of 5 organs including heart, lung, liver, pancreas, and kidney from most donors has become routine. Multiorgan procurement, however, is not an easy procedure, and it requires

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special technique and training. Sufficient donors are not available to perform on-site training for young surgeons. To prepare for the demand of increasing numbers of deceased donors in future, it is necessary to establish an educational program to ensure safe and expert multiorgan procurement. Herein, we report the development of an educational program and its efficacy in training of the liver procurement.

MATERIALS AND METHODS

Development of e-learning and simulation using pigs for multiorgan procurement are our main goal to establish the educational program. E-learning contains three dimensional computer graphic (3DCG) animations of the multiorgan procurement, explanation of both donor criteria and procurement procedure, and self-assessment examination.

It is crucial to elucidate the standard criteria for exact assessment of donors. From 1999 to 2013, 185 cases of donor procurement were performed, of which 160 cases of liver grafts were used for transplantation. The 25 risk factors of donors were analyzed in 138 adult cases of liver transplantation. The donor factors included date of procurement, hospital of procurement, admission date, age, sex, height, weight, body mass index, cause of death, length of hospital stay, length of cardiopulmonary resuscitation (>10 minutes), history of smoking, history of drinking, hemoglobin A1c, serum Na, serum blood urea nitrogen, serum creatinine, serum glucose, serum total bilirubin, serum aspartate aminotransferase, serum alanine aminotransferase, serum amylase, serum C-reactive protein, usage of high-dose dopamine (>15 mcg/kg/min), and usage of more than 2 vasopressors (from dopamine, dobutamine, noradrenalin, adrenalin, and vasopressin).

The 3DCG animation has been produced for liver and liver-pancreas procurement along with the scenario by Waseda University and Quality Experience Design Ltd, Tokyo. The solitary liver procurement procedure contained 2 sections: section A consisted of 11 sequences from opening the abdomen to cross-clamping the aorta, and section B consisted of 5 sequences from dissection of the common bile duct to procurement of the liver graft. The combined liver and pancreas procurement also contained 2 sections: section A (same as solitary liver procurement) and section C, which consisted of 10 sequences from mobilization of the duodenum to separation of liver from pancreas on the back table. The e-learning system was prepared to include 3DCG animations and explanation of both donor criteria and procurement procedure to educate a trainee prior to the simulation. This system will be open on the website for easy access to the trainees all across Japan.

Simulation for multiorgan procurement including heart, lung, liver, and pancreas was performed by each organ team in the Medical Innovation Institute of Technology Center, Johnson and Johnson, Inc. Japan (Sukagawa, Fukushima Prefecture, Japan) on August 10, 2013. The lectures for the procurement of each organ team were performed. The 3DCG animation was used for the liver procurement lecture. After that the self-assessment examination was performed.

A total of 41 trainees for liver procurement took the examination. The examination contained 7 questions related to both donor criteria and procurement of the liver; 4 questions (questions 1, 2, 5, 7) for complication asked the correct response to the donor status or complications during procurement procedure and 3 (questions 3,

Table 1. Contents of the Questions in Self-assessment Examination and Comparison of the Correct Answers Between Examinations in 2012 and in 2013

No.	QC	Questions	Answer Categories	Percentage of Correct Answers		P
				Exam 2012	Exam 2013	
1a	C	How would you respond when the blood pressure of the	Diagnosis	7.5	14.6	.259
1b		donor drops to 80/50 mm Hg under the dopamine drip at 5 μg/kg/min prior to the donor surgery?	Treatment	35.8	100.0	.0001
2a	C	How would you respond when you find a 3-cm diameter	Diagnosis	69.8	62.2	.215
2b		tumor on the surface of the liver during the donor surgery?	Treatment	22.6	24.4	.916
3a	A	How would you respond when you find the variant right	Procurement method	58.5	51.2	.314
3b		hepatic artery (the right hepatic artery from the superior mesenteric artery) under the circumstance that both liver and pancreas are planned to be procured?	Reconstruction method	32.1	61.0	.014
4a	A	How would you respond when you find the variant left	Procurement method	39.6	22.0	.023
4b		branch (the left hepatic artery from the left gastric artery) under the circumstance that both liver and pancreas are planned to be procured?	Reconstruction method	9.4	29.3	.022
5a	C	How would you respond when you get bleeding behind	Diagnosis	47.2	85.4	.0001
5b		the aorta during dissecting the abdominal aorta just above the bifurcation for cannulation?	Treatment	47.2	81.7	.002
6a	A	How would you respond when you find the variant renal	Place of cannulation	37.5	46.3	.644
6b		artery arising just above the aortic bifurcation during dissecting the abdominal aorta for cannulation?	Method of perfusion	12.5	19.5	.536
7a	C	How would you respond when you get bleeding behind	Method of hemostasis	27.5	31.7	.318
7b		the infraphrenic aorta during dissecting the aorta for cross-clamping?	Next step	40.0	48.8	.647
Total				34.8	48.4	.001

Abbreviations: QC, question category; C, complication; A, anatomy.

4, 6) for anatomy asked the correct response when you find an anatomical variation during procurement (Table 1). The result of the examination (exam 2013) was compared with the results after the lecture in 2012 (exam 2012) without using animation.

After demonstration of multiorgan procurement by the expert surgeons, the simulation for multiorgan procurement was performed by 97 trainees divided into 9 teams (each team consisted of approximately 10 young surgeons including 3 or 4 liver surgeons). After that, the survey was conducted.

Statistical analyses were performed with software SPSS version 21 (Japan IBM, Tokyo); univariate analysis with Fisher exact test and multivariate analysis with logistic regression analysis were used for risk factor analysis of donors, and t test was used for comparing examination results. P values less than .05 were considered statistically significant.

RESULTS

From the results from 138 cases of deceased donor liver transplantation in adults, 3 factors were independent for 3-month survival; cold ischemia time more than 10 hours (Exp (B) 61.3 (6.8–550.4), $P = .001$), Model for End-stage Liver Disease (MELD) score more than 20 (Exp (B) 4.9 (1.0–23.3), $P = .013$), and donor age more than 55 years (Exp (B) 6.0 (1.5–25.0), $P = .045$).

The results of the examinations showed that overall percentage of correct answers was significantly higher in exam 2013 than in exam 2012 (48.3% vs 32.7%; $P = .0001$; Table 1). While percentage of correct answers to the questions for complication was significantly higher in exam 2013 than in exam 2012 (54.5% vs 35.2%; $P = .0001$), there was no difference between exam 2013 and exam 2012 (36.0% vs 30.0%; $P = .271$) in percentage of the correct answers to the questions for anatomy.

Survey results from the 79 participants of the simulation of multiorgan procurement on August 10, 2013, showed participants in postgraduate 10 to 15 years were most predominant (37%), 52% of the participants could be operators in the any parts of the simulation, 94% agreed that the simulation was useful to improve their skills for procurement, 82% thought that they were prepared for real multiorgan procurement, 90% thought that they learned how to cooperate with other teams, and 99% thought that the simulation should be continued.

DISCUSSION

Three independent factors including cold ischemia time, MELD score, and donor age affected the early outcome in liver transplantation. Those were similar results compared to the one from earlier series of deceased donors [1]. Eliminating the recipients with high MELD score and elder donors is not practical. Minimizing cold ischemia time is the most certain and important method to improve early outcome. Close cooperation of the donor and recipient operations is critical to minimize cold ischemia time.

The results of the examination in 2013 improved significantly, compared to those in 2012, especially with the questions for complications. The 3DCG animation was used in the lecture prior to the simulation for the first time. The lecture with step-by-step explanation along with the animation and enriched contents of tips and pitfalls following each sequence of the animation can possibly be attributed to the improvement in the questions for complications in the 2013 examination. Instead, the explanation of anatomical variation was not sufficient because the animation was based on the regular anatomy in the limited time of the lecture. The e-learning has been prepared for the website and will be able to contain the enriched explanation for both complications and anatomical variations. A trainee could have enough time to study through e-learning and take the self-assessment examination prior to the simulation.

As apparent in the survey result, the simulation is one of the most important steps in the educational program to judge the self-assessment of surgical procedure as well as to learn how to cooperate with each other in multiorgan procurement. The survey results showed most of the participants thought that the simulation was useful. Financial support is the critical issue to continue the simulation. Either the government or hospitals registered for deceased donor transplantation should offer the sufficient support to maintain the quality of organ procurement in Japan.

In conclusion, the novel educational program could allow young surgeons to make precise assessment and perform the multiorgan procurement procedure. The establishment of this program could achieve safer donor operation, less graft failure, and better outcome of organ transplantation.

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REVIEW ARTICLE

Small-for-size syndrome in living-donor liver transplantation using a left lobe graft

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Abstract In living-donor liver transplantation with a left lobe graft, which can reduce the burden on the donor compared to right lobe graft, the main problem is small-for-size (SFS) syndrome. SFS syndrome is a multifactorial disease that includes aspects related to the graft size, graft quality, recipient factors and even technical issues. The main pathophysiology of SFS syndrome is the sinusoidal microcirculatory disturbance induced by shear stress, which is caused by excessive portal inflow into the smaller graft. The donor age, the presence of steatosis of the graft and a poor recipient status are all risk factors for SFS syndrome. To resolve SFS syndrome, portal inflow modulation, splenectomy, splenic artery modulation and outflow modulation have been developed. It is important to establish strict criteria for managing SFS syndrome. Using pharmacological interventions and/or therapeutic approaches that promote liver regeneration could increase the adequate outcomes in SFS liver transplantation. Left lobe liver transplantation could be adopted in Western countries to help resolve the organ shortage.

Keywords Small-for-size syndrome · Living-donor liver transplantation · Left lobe graft

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Introduction

Adult-to-adult living-donor liver transplantation (AA-LDLT) is an established treatment option for selected patients with end-stage liver disease. However, its widespread application is limited by the liver volume that can be safely resected from a living donor, because a sufficient volume is also required for the recipient. The use of a right lobe graft is widely recommended for AA-LDLT in Western countries because it can provide a sufficient volume for the recipient [1]. However, compared with a left lobe graft, a right lobe graft imposes a higher burden on the donor due to the smaller residual liver volume remaining in the donor [2]. Roll et al. [3] reported that there were 34 donor deaths worldwide based on a worldwide survey reported at the 2011 International Liver Transplant Society Meeting [4]. Of these donor deaths, 24 occurred in right lobe graft donors. In addition, left lobe donation leads to a lower rate of donor complications than right lobe donation for LDLT, especially biliary complications [3]. As a result, there is a renewed interest in the use of left lobe grafts to minimize the donor risk in Western countries [3, 5].

However, the main problem associated with using left lobe grafts in AA-LDLT is small-for-size (SFS) syndrome [6]. The size of the graft required for successful liver transplantation is 30–40 % of the expected liver volume for the recipient or 0.8–1.0 % of the body weight [7]. Excessive portal venous inflow is a determining factor for injury to endothelial cells and the hepatic parenchyma related to SFS syndrome [8, 9]. A better understanding of the pathophysiology of the SFS graft and improved surgical techniques has led to the development of logical approaches for improving the subsequent allograft function and patient survival [10, 11]. Splenectomy, splenic artery ligation and a permanent portacaval shunt (PC shunt) have been

developed in recent reports to resolve SFS syndrome [8, 12–14]. However, SFS syndrome cannot be completely avoided, even if an appropriate ratio of graft size to portal inflow is obtained. It is therefore believed that several factors might affect the development of SFS syndrome.

In this review, we discuss the pathophysiology, the risk factors for SFS syndrome and the current strategies for managing SFS syndrome to highlight the benefits of left lobe grafts to both the recipient and donor in AA-LDLT.

Definition of small-for-size graft syndrome

SFS grafts have been defined as those with graft-to-recipient weight ratios (GR/WR) of less than 0.8–1.0 %, or those with graft volume to standard liver volume (GV/SV) ratios of less than 30–40 % [6, 15]. However, SFS syndrome also depends on several factors other than the graft size, such as the graft quality, recipient factors and even technical issues. Therefore, the minimum graft volume has decreased and is different among transplant centers [16, 17]. SFS syndrome is clinically characterized by cholestasis, prolonged coagulopathy, intractable ascites and encephalopathy at the end of the first week after LDLT, which is diagnosed after the exclusion of other causes, such as technical complications and/or rejection or infections [6, 18–21]. The characteristic microscopic findings of SFS syndrome include hepatocyte ballooning, cholestasis and hemorrhagic necrosis around the central vein as a result of microcirculatory disturbances [22].

Although there is no consensus about the definition of SFS syndrome, several different definitions for SFS syndrome have been proposed [18, 19, 23]. Dahm et al. [18] proposed a more precise definition based on a survey of 20 expert surgeons in the fields of LDLT all over the world. They defined SFS syndrome as the presence of two of the following on 3 consecutive days: bilirubin >100 μmol/L (5.84 mg/dL), prothrombin time–international normalized ratio (PT-INR) >2, and grade 3 or 4 encephalopathy during the first postoperative week after the exclusion of other causes.

Pathophysiology (Fig. 1)

Excessive portal flow

Regarding the minimum requirement of a remnant liver for the functional demands after hepatectomy, a remnant liver of just 10 % can be sufficient to allow for survival in rats [24]. However, a larger volume is required in the clinical setting. A normal liver can tolerate a partial hepatectomy to 25–27 % of the residual volume [25–27]. The graft is subsequently subjected to the portal flow destined to the entire liver through a reduced micro-vascular bed [28]. The shear stress induced by the increased portal flow is

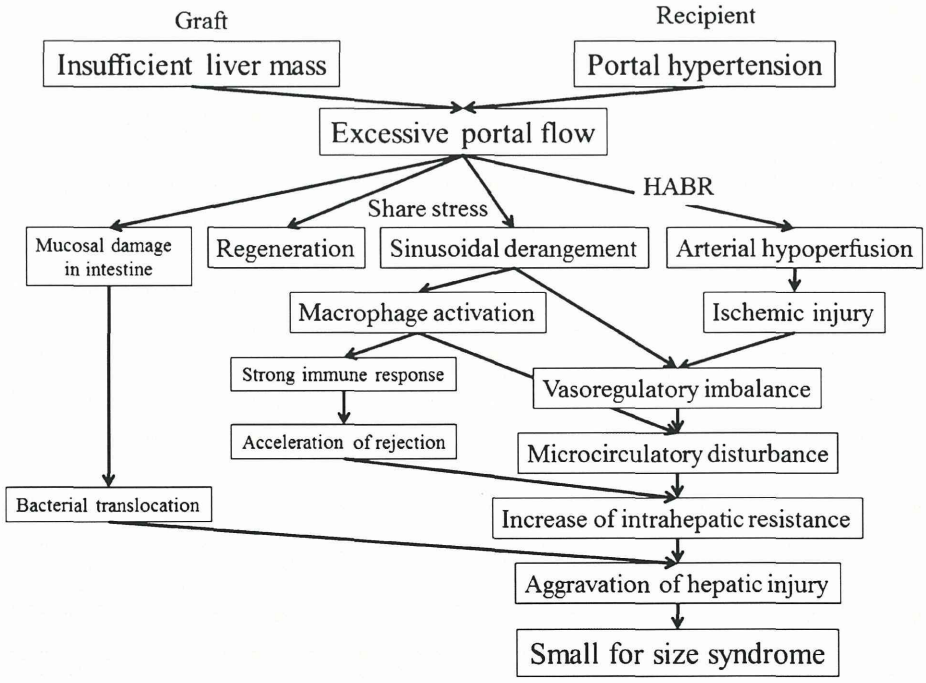

Fig. 1 The pathophysiology of small-for-size syndrome

considered to be a necessary stimulus for hepatic regeneration [29]; however, excessively increased portal flow may simultaneously cause sinusoidal endothelial injury. The recipient hemodynamics are also important, as cirrhotic recipients exhibit higher portal hypertension (PHT) than noncirrhotic patients [30]. PHT and hyperdynamic splanchnic circulation due to cirrhosis have also been suggested as contributory mechanisms for the pathogenesis of SFS syndrome. These factors induce excessive portal flow through the graft, which causes mechanical damage to the hepatic sinusoidal endothelium and microcirculatory disturbances.

In a rat model of partial liver transplantation, progressive mechanical damage related to excessive portal flow, resulting in sinusoidal congestion, tremendous swelling of the hepatocyte mitochondria, irregular large gaps between the sinusoidal lining cells and collapse of the space of Disse have been described [31]. Although the portal vein pressure (PVP) is considered to be a reliable predictor of graft failure, the PVP and portal vein flow (PVF) do not run parallel to each other. Sainz-Barriga et al. [32] reported that the evaluation of the PHT severity based on the PVP could be misleading because of the influence of the central venous pressure. They argued that the PVF and PVP should not be used individually to assess the hyperflow and PHT during liver transplantation.

The hepatic arterial buffer response (HABR)

Low hepatic arterial flow occurs secondary to excessive portal flow and is thought to be due to the so-called hepatic arterial buffer response (HABR) [33]. This response is mediated by the local concentrations of adenosine, which are controlled by the rate of washout into the portal blood to maintain constant total blood flow to the liver. In SFS grafts, an exaggerated HABR induced by excessive portal flow may contribute to ischemic injury [22, 34]. Kelly et al. [35] reported that an infusion of adenosine in 20 % standard liver grafts was able to inhibit the HABR and significantly improved the pathological changes in the allograft, which resulted in improved survival in a porcine model of SFS syndrome. Low hepatic arterial flow is associated with biliary ischemia, thus resulting in ischemic cholangitis and cholestasis.

Sinusoidal microcirculatory disturbances

Shear stress induced by excessive portal flow leads to an imbalance of vasoconstriction and vasorelaxation mediators [36], resulting in sinusoidal microcirculatory disturbances [37]. Man et al. [38] found that patients with SFS syndrome suffered from transient PHT after reperfusion, subsequent overexpression of endothelin-1 and a reduction in the level of nitric oxide in the plasma, together with the downregulation of heme oxygenase-1 and heat-shock protein 70 at the transcriptional level. In an experimental model of 30 % liver transplants, they showed that the imbalance of intragraft vasoregulatory genes (endothelin and the endothelin receptor), early overexpression of several adhesion molecules (IL-6, IL15 and TNFα), and the stress response (OH-1) play important roles in the sinusoidal injury leading to graft damage in SFS graft liver transplantation [39]. Increased formation of free radicals also occurs after SFS graft liver transplantation, which contributes to graft dysfunction and failure [40].

A strong immune response

Another factor to consider is the immunological status of the SFS liver allografts. Using rat models, Yang et al. [41] reported that early activation of macrophages as a result of graft injury might play an important role in the accelerated acute rejection process in SFS grafts. Moreover, they demonstrated that vascular endothelial growth factor (VEGF) production and VEGF receptor expression were increased in the SFS liver grafts during the early period after reperfusion; they also suggested that upregulated VEGF expression might enhance the monocyte and macrophage activities, which might contribute to microcirculatory damage, more severe inflammatory responses and accelerated acute rejection in SFS graft liver transplantation [42]. Based on our clinical experience, we reported an SFS graft case in which hepatic resistance was increased by acute rejection [43].

Intestinal mucosal damage

The intestinal mucosa was also impaired by PHT following SFS liver transplantation in swine [44]. PHT induced by major hepatic resection can increase bacterial translocation via the congestion and edema of the intestine due to increases in the intestinal capillary permeability and the endothelial cell membrane permeability [45, 46]. Bacterial infections constitute a major cause of mortality after major liver resection. It is easy to speculate that bacterial translocation may be caused by SFS graft liver transplantation, and could contribute to the poor outcomes in patients with SFS syndrome.

Risk factors for SFS liver transplantation

SFS syndrome does not depend solely on the graft size or PHT, because marginal grafts do not always result in graft failure. SFS syndrome is a multifactorial disease. Therefore, many other risk factors related to either the graft or the recipient can influence the outcome of SFS liver

transplantation. In other words, the addition of any other risk factors should be avoided.

Donor age

In deceased donor liver transplantation, an advanced donor age is associated with reduced graft and recipient survival [47, 48]. SFS liver transplantation from elderly donors is also a risk factor. Moon et al. [49] reported that the donor age was the only significant risk factor for poor graft survival in LDLT, and an SFS graft (GRWR <0.8 %) can be used safely when a recipient is receiving the graft from a donor younger than 44 years. Morioka et al. [50] reported that a higher donor age (≥50 years) appeared to be disadvantageous in terms of the survival outcomes in patients undergoing AA-LDLT. Similarly, Yoshida et al. [51] showed that recipients who received transplants from older donors (≥50 years) had significantly poorer survival rates. Ikegami et al. [52] demonstrated that the incidence of SFS syndrome was significantly greater in cases with LDLT from elderly donors; however, the morbidity and mortality rates were not influenced by the donor age. In another report from the same institution [53], the outcomes of left lobe LDLT were significantly improved by technical developments; however, the donor age (≥45 years) was still associated with the development of primary graft dysfunction.

Steatotic grafts

There are two types of steatosis: macrovesicular steatosis and microvesicular steatosis. In deceased donor liver transplantation, macrovesicular steatosis is an independent risk factor for poor graft survival [54]. However, livers with even severe microvesicular steatosis can be reliably used for transplantation without fear of high rates of primary nonfunction [55]. There have been a few reports about steatosis in the LDLT setting. Hayashi et al. reported that the early graft function after LDLT was similar in cases with mild and moderate steatosis, but that severe steatosis was significantly associated with poor graft function and survival [56]. Similarly, Soejima et al. [57] reported that the use of a fatty liver graft up to a moderate level of steatosis can be justified in LDLT. It is well known that steatotic grafts with longer cold ischemic times are associated with poorer graft function and survival [58]. Compared with cadaveric grafts, this situation may be less important in LDLT because of the reduced cold ischemia time. There have been no other studies regarding the relationship between SFS syndrome and steatosis. However, SFS syndrome is multifactorial, as mentioned above. It is therefore desirable to avoid steatotic grafts, particularly if the graft is small.

Poor recipient status

Taking the pathophysiology of SFS syndrome into consideration, the pre-transplant recipient condition is a risk factor for SFS syndrome, such as a severe status of preoperative liver disease [59] and/or severe cirrhosis [2]. Lei et al. [60] revealed that the Model for End-stage Liver Disease (MELD) score was one of the risk factors for the development of SFS syndrome. Similarly, MELD scores greater than 31 [50] or 21 [51] appeared to be disadvantageous in terms of the survival outcomes in patients undergoing LDLT. However, recent studies revealed that it is safe to use SFS grafts even in high pre-MELD score recipients [61, 62]. The improvements in surgical techniques and intensive care, the introduction of treatment strategies for SFS syndrome and the strict selection of listing criteria may improve the outcome of SFS liver graft transplantation even in high MELD score recipients.

Current strategies

Inflow modulation

Since Boillot et al. [12] reported the first successful case in which SFS syndrome was prevented with a portocaval shunt, several surgeons have reported the successful treatment of SFS syndrome with inflow modulation. Yamada et al. [63] showed that a selective portocaval shunt based on the PVP is effective, and results in excellent patient and graft survival with the avoidance of SFS syndrome in grafts with a greater than 0.6 % GRWR. However, we reported that, while the portocaval shunt would overcome SFS syndrome in the early period of LDLT, it would cause graft atrophy and dysfunction through the steal phenomenon at later times [43]. Thus, closing the shunt is important in the late period of LDLT. To resolve the problems associated with using a conventional shunt, we developed a transient portocaval shunt technique using an Endoloop [64]. Another report also showed the usefulness of occluding a hemiportocaval shunt using an endovascular technique [65]. Similarly, the size of the portocaval shunt that is required to prevent SFS syndrome has not been clear. In the swine model, Yagi et al. observed that inadequate portal flow provided by a large portocaval shunt impaired not only the graft survival rates, but also the patient survival rates [44]. Hessheimer et al. [66] also demonstrated that a portocaval shunt that maintains the PVF at approximately twice its baseline value produced a favorable outcome after SFS liver transplantation, avoiding endothelial injury due to either portal hyperperfusion or hypoperfusion because of excess shunting in a swine 30 % SFS liver transplant model. In recent years, several successful treatments with