data were entered into a Microsoft Excel spreadsheet and analyzed with JMP version 10.0 (SAS Institute Inc., Cary, NC, United States). Patient and graft survival estimates were obtained using the Kaplan-Meier method. For survival analysis, failure was defined as occurring on the date of graft removal or death. $P < .05$ was considered statistically significant. This study was approved by the institutional review board.

RESULTS

Five programs provided data on 24 grafts in 21 patients who received transplants between April 1, 1996, and June 30, 2012, in Japan. The participation rate was 100%. All intestinal transplantations performed in Japan are captured in the registry database. All patients were followed until patient death. Twelve grafts were obtained from living donors, and 12 involved deceased donors. The annual number of intestinal transplantations, according to organ donation type, is shown in Fig 1.

The age distribution of the recipients is shown in Fig 2. The youngest recipient was 8 months old. The causes of intestinal failure requiring intestinal transplantation are shown in Fig 3.

Most patients ($n = 23$) received isolated intestinal transplants. There was only 1 case of simultaneous liver-intestinal transplantation from 2 living related donors. All patients were on tacrolimus maintenance therapy.

Graft and patient overall survival as of June 2012 are shown in Kaplan-Meier plots (Fig 4A and B, respectively). The 1-year and 5-year patient survival rates were 86% and 68%, respectively.

Graft survival has improved over the last few years. The 1- and 5-year graft survival rates were 83% and 73% for 2006 to 2012 versus 66% and 44% for 1996 to 2005 ($P = .12$), as shown in Fig 5A. The 1- and 5-year patient survival rates were 92% and 83% for 2006 to 2012 versus 75% and 50% for 1996 to 2005 ($P = .16$), as shown in Fig 5B.

Graft function in terms of PN dependence was excellent. After intestinal transplantation, 77% of patients became PN-free, although 75% require continuous or intermittent IV fluid support. Most recipients stopped parenteral supplementation, eat, and have resumed normal activities.

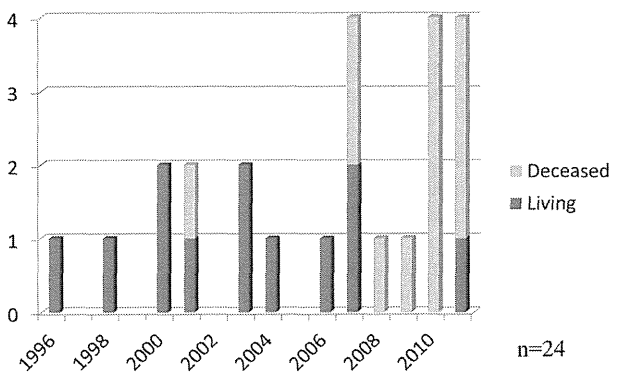

Fig 1. Number of intestinal transplantations per year in Japan, 1996 to 2010.

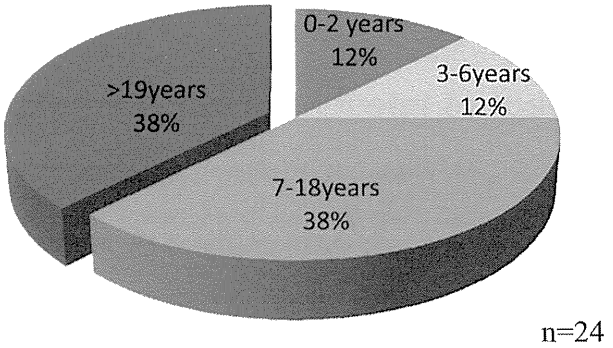

Fig 2. Age of intestinal transplant recipients.

DISCUSSION

Patients with intestinal failure are at risk for numerous complications, especially PN-related complications. For example, loss of venous access and intestinal failure-associated liver disease are still major problems for patients with intestinal failure because they are potentially life-threatening [1].

As outcomes of intestinal transplantation have improved, it has become the definitive treatment for patients with intestinal failure who cannot tolerate PN. Over the past decade, intestinal transplantation has become accepted as standard therapy for patients with life-threatening complications of PN in many countries [2,3].

The 2011 report of the intestinal transplant registry confirmed that intestinal transplantation has become a definitive therapeutic option for patients with intestinal failure. By 2011, 2611 intestinal transplantations have been performed throughout the world in 79 participating centers [3].

On the other hand, only 24 intestinal transplantations have been performed in Japan. The number is relatively small, although it is estimated that nationwide approximately 100 patients require intestinal transplantations [4]. In the Japanese experience, the 2- and 20-year overall patient survival rates are 86% and 68%. The 1-year survival

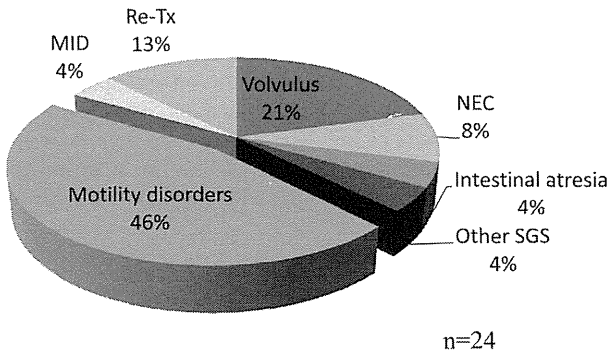

Fig 3. Indications for intestinal transplantation. NEC, necrotizing enterocolitis; SGS, short gut syndrome; MID, microvillus inclusion disease; Re-Tx, retransplantation.

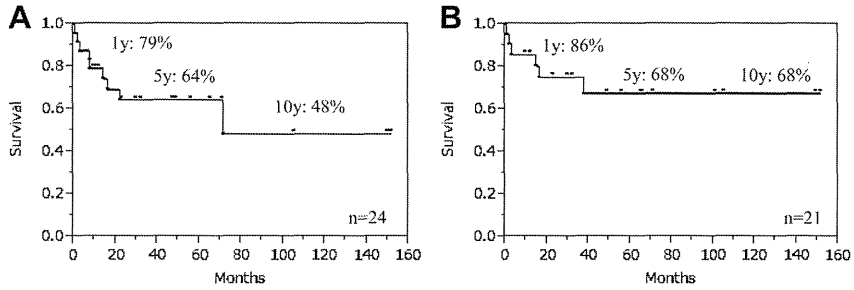

Fig 4. **(A)** Overall graft survival. **(B)** Overall patient survival.

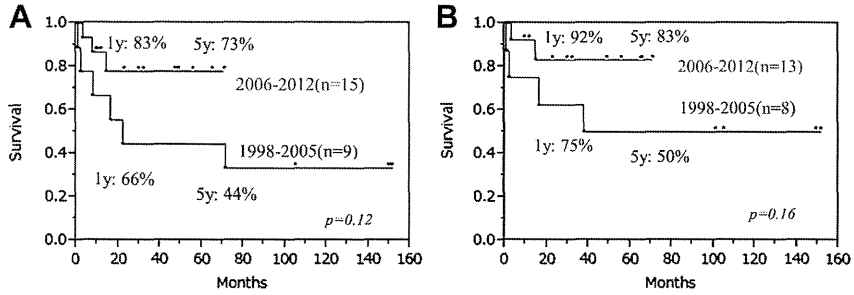

Fig 5. **(A)** Graft survival by era. **(B)** Patient survival by era.

rate has been 92% since 2006. These are considered acceptable results for the treatment of intestinal failure. Our results in Japan are comparable with results worldwide, even though there are only 1 or 2 cases performed per year in Japan, compared to over 100 intestinal transplantations performed in the world each year. In our opinion, patients with intestinal failure should be treated with intestinal transplantation in Japan, as well as in other countries, when feasible.

There were 2 major reasons for the low number of intestinal transplantations in Japan. One reason is the lack of available organs. For a long time, relatively few donations from deceased donors were obtainable in Japan. As with other solid organs, most intestinal transplantations in Japan are performed with living related donors. Although the situation has changed due to the new Act on Organ Transplantation, which went into effect in 2010, the number of deceased donations has not increased dramatically.

The financial barrier is the other, more profound reason preventing the greater use of intestinal transplantation in Japan. Since the procedure is not covered by health insurance, either the patient or the transplant center must pay the considerable costs out of pocket.

In conclusion, intestinal transplantation has become an effective therapy for patients with intestinal failure who cannot tolerate PN. After 2006, patient and graft survival rates have approached rates associated with standard treatment for end-stage intestinal failure. Further improvements are expected with early referral due to suitable donor organ and pretransplant management.

REFERENCES

[1] Maroulis J, Kalfarentzos F. Complications of parenteral nutrition at the end of the century. Clin Nutr 2000;19:295–304.

[2] Magee JC, Krishnan SM, Benfield MR, et al. Pediatric transplantation in the United States, 1997-2006. Am J Transplant 2008;8(4 Pt 2):935–45.

[3] Grant D. Small Bowel Transplant Registry. Paper presented at: 12th International Small Bowel Transplant Symposium, Washington DC, USA, September 15-18, 2011. Washington.

[4] Ueno T, Wada M, Hoshino M, Sakamoto K, Furukawa S, Fukuzawa H, M. A national survey of patients with intestinal motility disorder who are potential candidate for intestinal transplantation in Japan. Transplant Proc 2013;45:2029–31.

Surg Today
DOI 10.1007/s00595-014-0945-x

REVIEW ARTICLE

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

Masahiko Taniguchi · Tsuyoshi Shimamura · Satoru Todo · Hiroyuki Furukawa

Received: 27 February 2014 / Accepted: 12 May 2014

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

M. Taniguchi (✉) · H. Furukawa
Division of Gastroenterologic and General Surgery, Department of Surgery, Asahikawa Medical College, 2-1 Midorigaoka-Higashi, Asahikawa 078-8510, Japan
e-mail: tonny@isis.ocn.ne.jp; m-tani@asahikawa-med.ac.jp

T. Shimamura
Division of Organ Transplantation, Hokkaido University Hospital, Sapporo, Japan

S. Todo
Research Institute of St. Mary's Hospital, Kurume, Japan

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

Published online: 05 June 2014

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

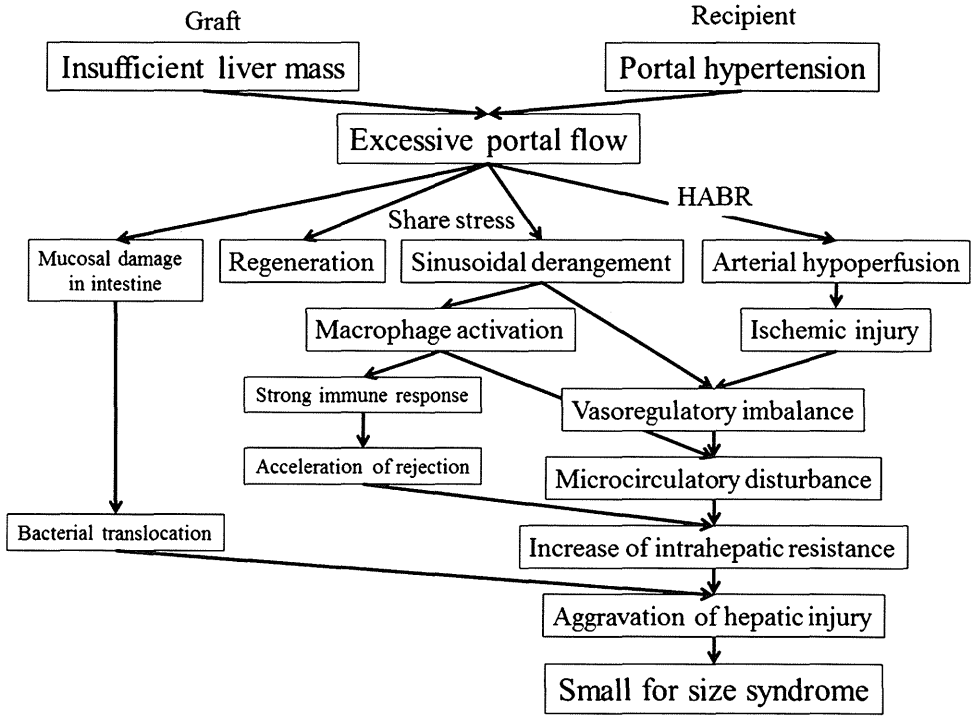

Fig. 1 The pathophysiology of small-for-size syndrome

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

other portosystemic shunts have been reported, including the transjugular intrahepatic portosystemic shunt [67], the interposed obliterated ligamentum teres hepatis [68] and a mesorenal shunt between the inferior mesenteric vein and the left renal vein. In the US, left lobe AA-LDLT has recently been attempted using hemiportocaval shunts, with comparable results [69].

Splenectomy and splenic artery modulation

Another way to achieve inflow modulation is to control the splanchnic circulation, such as through splenic artery ligation, splenic artery embolization or splenectomy. Prophylactic splenic artery modulation (preoperative embolization or intraoperative ligation) seemed to relieve portal hyperperfusion injury and contributed to the improvement of the post-transplantation prognosis through liver regeneration [70]. Such treatment may even be useful after the diagnosis of established SFS syndrome after LDLT, because an Italian group reported successful early splenic artery embolization within the first week after LDLT [71]. Another group also reported that delayed splenic artery occlusion by intraoperative splenic artery ligation or radiological splenic artery coiling improved the SFS graft syndrome [72]. For the treatment of SFS syndrome that occurred despite splenic artery ligation, Ozden et al. [73] have reported success using somatostatin and propranolol.

It is well known that simultaneous splenectomy is beneficial for overcoming SFS syndrome [14]. Furthermore, Ren et al. [74] showed that splenectomy leads to the resolution of liver function and improves the liver regeneration ratio after different degrees of massive hepatectomy in a rat model. These effects may be mediated through the enhancement of hepatic oxygen delivery and consumption, which augment liver regeneration. Splenectomy has another benefit for the treatment of pancytopenia in cases with hepatitis C virus (HCV) treatment [75]. However, a Japanese group found that the modulation of the graft portal inflow or splenectomy was not needed for successful left lobe graft LDLT when the PVP did not exceed 25 mmHg after transplantation [76, 77]. In deceased donor liver transplantation, concomitant splenectomy with DDLT was not recommended due to its potential for septic complications [78]. It is important to establish strict selection criteria and prophylaxis for the septic complications of splenectomy.

Outflow modulation

Hepatic vein reconstruction is one of the most essential steps for preventing SFS syndrome, because outflow insufficiency induces liver congestion, resulting in graft failure [79]. End-to-end anastomosis of the hepatic veins is fundamental for preventing an outflow occlusion. Graft regeneration tends to shift a graft's position toward the right subphrenic space. This shift leads to the distortion of the middle and left hepatic veins. To ensure adequate hepatic venous flow, it is necessary to obtain a wide ostium and sufficient length of the hepatic vein for anastomosis. To achieve this objective, venoplasty of the hepatic veins of the graft and the recipient is invaluable. Especially in a left lobe graft without the trunk of the middle hepatic vein, venoplasty between the middle and left hepatic vein might be necessary to prevent graft congestion in segment IV. Suehiro et al. [80] reported that hepatic vein–inferior vena cava (HV-IVC) reconstruction with graft venoplasty and IVC cavoplasty was useful for preventing outflow block. Color Doppler ultrasonography or a hepatic arterial clamping test is useful for evaluating the need for middle hepatic vein reconstruction [81]. If the graft has a large short hepatic vein, reconstruction of this vein is important to prevent the congestion of the caudate lobe. Yamauchi et al. [82] demonstrated new techniques with single-orifice vein reconstruction for venous drainage in left liver plus caudate lobe grafts. In a recent study, obtaining images of the anatomical interrelationships of the hepatic veins using preoperative three-dimensional computed tomography scanning was helpful for surgeons to determine the appropriate technique or form for the hepatic venoplasty [83].

Pharmacological interventions in experimental models

Based on its pathophysiology, many pharmacological interventions have been reported to improve the outcome of SFS syndrome in animal models. Several studies have targeted vascular regulation to modulate the portal inflow, including the following: prostaglandin E1 [84, 85]; FK409, a nitric oxide donor [86]; an endothelin receptor-A antagonist [87]; an adenosine A2a receptor agonist [88]; Olprinone, a selective phosphodiesterase III inhibitor [89]; heme oxygenase-1 [90] and MnTBAP, a superoxide dismutase mimetic [91]. Therapeutic approaches that promote liver regeneration, such as serotonin through its action on receptor-2B [92], overexpression of redox factor 1 [93] and inhibition of nuclear factor kappa B activation [94] also protected SFS liver grafts. Recently, mesenchymal stem cells have been studied to determine their role in stimulating liver regeneration. In particular, Fouraschen et al. showed that mesenchymal stem cell-secreted factors were effective at stimulating liver regeneration after surgical resection by influencing the expression levels of cytokines and growth factors relevant for cell proliferation, angiogenesis and anti-inflammatory responses in a rat model of 70 % partial hepatectomy. Mesenchymal stem cell-

secreted factors may represent a feasible new strategy for promoting liver regeneration in patients with SFS liver grafts. From another point of view, newly developed preservation solutions may improve the survival after SFS graft transplantation. For example, Yagi et al. [95] maintained that improvement of microcirculatory disturbances with a novel preservation solution could maintain the graft viability, and could thus ameliorate poor outcomes of SFS grafts in a rat model (Fig. 1).

Conclusions

Left lobe liver transplantation is a well-established procedure in Japan, although SFS syndrome is an unavoidable phenomenon for small grafts. In recent years, the rate of graft failure due to SFS syndrome has been decreased because of the development of new strategies to prevent SFS syndrome and improved surgical techniques. A better understanding of the pathophysiology of SFS syndrome should also result in better outcomes. To achieve excellent outcomes in LDLT with small grafts, it is essential to avoid the addition of any other risk factors that can increase the intrahepatic resistance, such as acute cellular rejection and cholangitis. Moreover, using pharmacological interventions and/or therapeutic approaches that promote liver regeneration by stem cells should improve the outcomes of SFS liver transplantation. To resolve the organ shortage, left lobe liver transplantation could be adopted even in Western countries.

Acknowledgments There was no support provided for this study.

References

1. Trotter JF, Wachs M, Everson GT, Kam I. Adult-to-adult transplantation of the right hepatic lobe from a living donor. N Engl J Med. 2002;346(14):1074–82. doi:10.1056/NEJMra011629.
2. Soejima Y, Shimada M, Suehiro T, Hiroshige S, Ninomiya M, Shiotani S, et al. Outcome analysis in adult-to-adult living donor liver transplantation using the left lobe. Liver Transplant. 2003;9(6):581–6. doi:10.1053/jlts.2003.50114.
3. Roll GR, Parekh JR, Parker WF, Siegler M, Pomfret EA, Ascher NL, et al. Left hepatectomy versus right hepatectomy for living donor liver transplantation: shifting the risk from the donor to the recipient. Liver Transplant. 2013;19(5):472–81. doi:10.1002/lt.23608.
4. Cheah YL, Simpson MA, Pomposelli JJ, Pomfret EA. Incidence of death and potentially life-threatening near-miss events in living donor hepatic lobectomy: a world-wide survey. Liver Transplantation. 2013;19(5):499–506. doi:10.1002/lt.23575.
5. Troisi RI, Wojcicki M, Tomassini F, Houtmeyers P, Vanlander A, Berrevoet F, et al. Pure laparoscopic full-left living donor hepatectomy for calculated small-for-size LDLT in adults: proof of concept. Am J Transplant. 2013;13(9):2472–8. doi:10.1111/ajt.12362.
6. Kiuchi T, Kasahara M, Uryuhara K, Inomata Y, Uemoto S, Asonuma K, et al. Impact of graft size mismatching on graft prognosis in liver transplantation from living donors. Transplantation. 1999;67(2):321–7.
7. Kawasaki S, Makuuchi M, Matsunami H, Hashikura Y, Ikegami T, Nakazawa Y, et al. Living related liver transplantation in adults. Ann Surg. 1998;227(2):269–74.
8. Masetti M, Siniscalchi A, De Pietri L, Braglia V, Benedetto F, Di Cautero N, et al. Living donor liver transplantation with left liver graft. Am J Transplant. 2004;4(10):1713–6. doi:10.1111/j.1600-6143.2004.00548.xAJT548.
9. Shimamura T, Taniguchi M, Jin MB, Suzuki T, Matsushita M, Furukawa H, et al. Excessive portal venous inflow as a cause of allograft dysfunction in small-for-size living donor liver transplantation. Transplant Proc. 2001;33(1–2):1331.
10. Boillot O, Sagnard P, Guillaud O, Ber CE, Pouyet M, Dumortier J. Adult left liver transplantation from split livers and living donors: a 14-year single-center experience. Clin Transplant. 2013;27(4):571–81. doi:10.1111/ctr.12162.
11. Soejima Y, Shirabe K, Taketomi A, Yoshizumi T, Uchiyama H, Ikegami T, et al. Left lobe living donor liver transplantation in adults. Am J Transplant. 2012;12(7):1877–85. doi:10.1111/j.1600-6143.2012.04022.x.
12. Boillot O, Delafosse B, Mechet I, Boucaud C, Pouyet M. Small-for-size partial liver graft in an adult recipient; a new transplant technique. Lancet. 2002;359(9304):406–7. doi:10.1016/S0140-6736(02)07593-1.
13. Troisi R, Ricciardi S, Smeets P, Petrovic M, Van Maele G, Colle I, et al. Effects of hemi-portocaval shunts for inflow modulation on the outcome of small-for-size grafts in living donor liver transplantation. Am J Transplant. 2005;5(6):1397–404. doi:10.1111/j.1600-6143.2005.00850.x.
14. Yoshizumi T, Taketomi A, Soejima Y, Ikegami T, Uchiyama H, Kayashima H, et al. The beneficial role of simultaneous splenectomy in living donor liver transplantation in patients with small-for-size graft. Transplant Int. 2008;21(9):833–42. doi:10.1111/j.1432-2277.2008.00678.x.
15. Emond JC, Renz JF, Ferrell LD, Rosenthal P, Lim RC, Roberts JP, et al. Functional analysis of grafts from living donors. Implications for the treatment of older recipients. Ann Surg. 1996;224(4):544–52 (discussion 52-4).
16. Kaido T, Mori A, Ogura Y, Hata K, Yoshizawa A, Iida T, et al. Lower limit of the graft-to-recipient weight ratio can be safely reduced to 0.6% in adult-to-adult living donor liver transplantation in combination with portal pressure control. Transplant Proc. 2011;43(6):2391–3. doi:10.1016/j.transproceed.2011.05.037.
17. Selzner M, Kashfi A, Cattral MS, Selzner N, Greig PD, Lilly L, et al. A graft to body weight ratio less than 0.8 does not exclude adult-to-adult right-lobe living donor liver transplantation. Liver Transplant. 2009;15(12):1776–82. doi:10.1002/lt.21955.
18. Dahm F, Georgiev P, Clavien PA. Small-for-size syndrome after partial liver transplantation: definition, mechanisms of disease and clinical implications. Am J Transplant. 2005;5(11):2605–10. doi:10.1111/j.1600-6143.2005.01081.x.
19. Soejima Y, Taketomi A, Yoshizumi T, Uchiyama H, Harada N, Ijichi H, et al. Feasibility of left lobe living donor liver transplantation between adults: an 8-year, single-center experience of 107 cases. Am J Transplant. 2006;6(5 Pt 1):1004–11. doi:10.1111/j.1600-6143.2006.01284.x.
20. Sugawara Y, Makuuchi M. Small-for-size graft problems in adult-to-adult living-donor liver transplantation. Transplantation. 2003;75(3 Suppl):S20–2. doi:10.1097/01.TP.0000046616.76542.DF.
21. Lo CM, Fan ST, Chan JK, Wei W, Lo RJ, Lai CL. Minimum graft volume for successful adult-to-adult living donor liver

transplantation for fulminant hepatic failure. Transplantation. 1996;62(5):696–8.
22. Demetris AJ, Kelly DM, Eghtesad B, Fontes P, Wallis Marsh J, Tom K, et al. Pathophysiologic observations and histopathologic recognition of the portal hyperperfusion or small-for-size syndrome. Am J Surg Pathol. 2006;30(8):986–93.
23. Hill MJ, Hughes M, Jie T, Cohen M, Lake J, Payne WD, et al. Graft weight/recipient weight ratio: how well does it predict outcome after partial liver transplants? Liver Transplant. 2009;15(9):1056–62. doi:10.1002/lt.21846.
24. Chang TH, Hakamada K, Toyoki Y, Tsuchida S, Sasaki M. Expression of MRP2 and MRP3 during liver regeneration after 90% partial hepatectomy in rats. Transplantation. 2004;77(1):22–7. doi:10.1097/01.TP.0000089234.93366.6D.
25. Ferrero A, Vigano L, Polastri R, Muratore A, Eminefendic H, Regge D, et al. Postoperative liver dysfunction and future remnant liver: where is the limit? Results of a prospective study. World J Surg. 2007;31(8):1643–51. doi:10.1007/s00268-007-9123-2.
26. Schindl MJ, Redhead DN, Fearon KC, Garden OJ, Wigmore SJ, Edinburgh Liver S, et al. The value of residual liver volume as a predictor of hepatic dysfunction and infection after major liver resection. Gut. 2005;54(2):289–96.
27. Vauthey JN, Chaoui A, Do KA, Bilimoria MM, Fenstermacher MJ, Charnsangavej C, et al. Standardized measurement of the future liver remnant prior to extended liver resection: methodology and clinical associations. Surgery. 2000;127(5):512–9. doi:10.1067/msy.2000.105294.
28. Glanemann M, Eipel C, Nussler AK, Vollmar B, Neuhaus P. Hyperperfusion syndrome in small-for-size livers. Eur Surg Res Europaische chirurgische Forschung Recherches chirurgicales europeennes. 2005;37(6):335–41. doi:10.1159/000090333.
29. Schoen JM, Wang HH, Minuk GY, Lautt WW. Shear stress-induced nitric oxide release triggers the liver regeneration cascade. Nitric Oxide. 2001;5(5):453–64. doi:10.1006/niox.2001.0373.
30. Yagi S, Iida T, Taniguchi K, Hori T, Hamada T, Fujii K, et al. Impact of portal venous pressure on regeneration and graft damage after living-donor liver transplantation. Liver Transplant. 2005;11(1):68–75. doi:10.1002/lt.20317.
31. Man K, Lo CM, Ng IO, Wong YC, Qin LF, Fan ST, et al. Liver transplantation in rats using small-for-size grafts: a study of hemodynamic and morphological changes. Arch Surg. 2001;136(3):280–5.
32. Sainz-Barriga M, Scudeller L, Costa MG, de Hemptinne B, Troisi RI. Lack of a correlation between portal vein flow and pressure: toward a shared interpretation of hemodynamic stress governing inflow modulation in liver transplantation. Liver Transplant. 2011;17(7):836–48. doi:10.1002/lt.22295.
33. Lautt WW, Legare DJ, d'Almeida MS. Adenosine as putative regulator of hepatic arterial flow (the buffer response). Am J Physiol. 1985;248(3 Pt 2):H331–8.
34. Smyrniotis V, Kostopanagiotou G, Kondi A, Gamaletsos E, Theodoraki K, Kehagias D, et al. Hemodynamic interaction between portal vein and hepatic artery flow in small-for-size split liver transplantation. Transplant Int. 2002;15(7):355–60. doi:10.1007/s00147-002-0425-x.
35. Kelly DM, Zhu X, Shiba H, Irefin S, Trenti L, Cocieru A, et al. Adenosine restores the hepatic artery buffer response and improves survival in a porcine model of small-for-size syndrome. Liver Transplant. 2009;15(11):1448–57. doi:10.1002/lt.21863.
36. Palmes D, Minin E, Budny T, Uhlmann D, Armann B, Stratmann U, et al. The endothelin/nitric oxide balance determines small-for-size liver injury after reduced-size rat liver transplantation. Virchows Archiv. 2005;447(4):731–41. doi:10.1007/s00428-005-0006-3.
37. Li J, Liang L, Ma T, Yu X, Chen W, Xu G, et al. Sinusoidal microcirculatory changes after small-for-size liver transplantation in rats. Transplant Int. 2010;23(9):924–33. doi:10.1111/j.1432-2277.2010.01058.x.
38. Man K, Fan ST, Lo CM, Liu CL, Fung PC, Liang TB, et al. Graft injury in relation to graft size in right lobe live donor liver transplantation: a study of hepatic sinusoidal injury in correlation with portal hemodynamics and intragraft gene expression. Ann Surg. 2003;237(2):256–64. doi:10.1097/01.SLA.0000048976.11824.67.
39. Man K, Lo CM, Lee TK, Li XL, Ng IO, Fan ST. Intragraft gene expression profiles by cDNA microarray in small-for-size liver grafts. Liver Transplant. 2003;9(4):425–32. doi:10.1053/jlts.2003.50066.
40. Zhong Z, Connor HD, Froh M, Bunzendahl H, Lind H, Lehnert M, et al. Free radical-dependent dysfunction of small-for-size rat liver grafts: prevention by plant polyphenols. Gastroenterology. 2005;129(2):652–64. doi:10.1016/j.gastro.2005.05.060.
41. Yang ZF, Ho DW, Chu AC, Wang YQ, Fan ST. Linking inflammation to acute rejection in small-for-size liver allografts: the potential role of early macrophage activation. Am J Transplant. 2004;4(2):196–209.
42. Yang ZF, Poon RT, Luo Y, Cheung CK, Ho DW, Lo CM, et al. Up-regulation of vascular endothelial growth factor (VEGF) in small-for-size liver grafts enhances macrophage activities through VEGF receptor 2-dependent pathway. J Immunol. 2004;173(4):2507–15.
43. Oura T, Taniguchi M, Shimamura T, Suzuki T, Yamashita K, Uno M, et al. Does the permanent portacaval shunt for a small-for-size graft in a living donor liver transplantation do more harm than good? Am J Transplant. 2008;8(1):250–2. doi:10.1111/j.1600-6143.2007.02045.x.
44. Yagi S, Iida T, Hori T, Taniguchi K, Nagahama M, Isaji S, et al. Effect of portal haemodynamics on liver graft and intestinal mucosa after small-for-size liver transplantation in swine. Eur Surg Res Europaische chirurgische Forschung Recherches chirurgicales europeennes. 2012;48(3):163–70. doi:10.1159/000338622.
45. Wang X, Andersson R, Soltesz V, Wang L, Bengmark S. Effect of portal hypertension on bacterial translocation induced by major liver resection in rats. Eur J Surg Acta chirurgica. 1993;159(6–7):343–50.
46. Wang XD, Guo WD, Wang Q, Andersson R, Ekblad E, Soltesz V, et al. The association between enteric bacterial overgrowth and gastrointestinal motility after subtotal liver resection or portal vein obstruction in rats. Eur J Surg Acta chirurgica. 1994;160(3):153–60.
47. Busquets J, Xiol X, Figueras J, Jaurrieta E, Torras J, Ramos E, et al. The impact of donor age on liver transplantation: influence of donor age on early liver function and on subsequent patient and graft survival. Transplantation. 2001;71(12):1765–71.
48. Lake JR, Shorr JS, Steffen BJ, Chu AH, Gordon RD, Wiesner RH. Differential effects of donor age in liver transplant recipients infected with hepatitis B, hepatitis C and without viral hepatitis. Am J Transplant. 2005;5(3):549–57. doi:10.1111/j.1600-6143.2005.00741.x.
49. Moon JI, Kwon CH, Joh JW, Jung GO, Choi GS, Park JB, et al. Safety of small-for-size grafts in adult-to-adult living donor liver transplantation using the right lobe. Liver Transplant. 2010;16(7):864–9. doi:10.1002/lt.22094.
50. Morioka D, Egawa H, Kasahara M, Ito T, Haga H, Takada Y, et al. Outcomes of adult-to-adult living donor liver transplantation: a single institution's experience with 335 consecutive cases. Ann Surg. 2007;245(2):315–25. doi:10.1097/01.sla.0000236600.24667.a4.

51. Yoshida R, Iwamoto T, Yagi T, Sato D, Umeda Y, Mizuno K, et al. Preoperative assessment of the risk factors that help to predict the prognosis after living donor liver transplantation. World J Surg. 2008;32(11):2419–24. doi:10.1007/s00268-008-9715-5.
52. Ikegami T, Taketomi A, Ohta R, Soejima Y, Yoshizumi T, Shimada M, et al. Donor age in living donor liver transplantation. Transplant Proc. 2008;40(5):1471–5. doi:10.1016/j.transproceed.2008.02.084.
53. Ikegami T, Shirabe K, Soejima Y, Yoshizumi T, Uchiyama H, Yamashita Y, et al. Strategies for successful left-lobe living donor liver transplantation in 250 consecutive adult cases in a single center. J Am Coll Surg. 2013;216(3):353–62. doi:10.1016/j.jamcollsurg.2012.11.011.
54. Spitzer AL, Lao OB, Dick AA, Bakthavatsalam R, Halldorson JB, Yeh MM, et al. The biopsied donor liver: incorporating macrosteatosis into high-risk donor assessment. Liver Transplant. 2010;16(7):874–84. doi:10.1002/lt.22085.
55. Fishbein TM, Fiel MI, Emre S, Cubukcu O, Guy SR, Schwartz ME, et al. Use of livers with microvesicular fat safely expands the donor pool. Transplantation. 1997;64(2):248–51.
56. Hayashi M, Fujii K, Kiuchi T, Uryuhara K, Kasahara M, Takatsuki M, et al. Effects of fatty infiltration of the graft on the outcome of living-related liver transplantation. Transplant Proc. 1999;31(1–2):403.
57. Soejima Y, Shimada M, Suehiro T, Kishikawa K, Yoshizumi T, Hashimoto K, et al. Use of steatotic graft in living-donor liver transplantation. Transplantation. 2003;76(2):344–8. doi:10.1097/01.TP.0000071205.52835.A4.
58. Busuttil RW, Tanaka K. The utility of marginal donors in liver transplantation. Liver Transplant. 2003;9(7):651–63. doi:10.1053/jlts.2003.50105.
59. Ben-Haim M, Emre S, Fishbein TM, Sheiner PA, Bodian CA, Kim-Schluger L, et al. Critical graft size in adult-to-adult living donor liver transplantation: impact of the recipient's disease. Liver Transplant. 2001;7(11):948–53. doi:10.1053/jlts.2001.29033.
60. Lei JY, Wang WT, Yan LN. Risk factors of SFSS in adult-to-adult living donor liver transplantation using the right liver: a single-center analysis of 217 cases. Hepatogastroenterology. 2012;59(117):1491–7. doi:10.5754/hge11634.
61. Li H, Li B, Wei Y, Yan L, Wen T, Xu M, et al. Outcome of using small-for-size grafts in living donor liver transplantation recipients with high model for end-stage liver disease scores: a single center experience. PLoS One. 2013;8(9):e74081. doi:10.1371/journal.pone.0074081.
62. Yi NJ, Suh KS, Lee HW, Shin WY, Kim J, Kim W, et al. Improved outcome of adult recipients with a high model for end-stage liver disease score and a small-for-size graft. Liver Transplant. 2009;15(5):496–503. doi:10.1002/lt.21606.
63. Yamada T, Tanaka K, Uryuhara K, Ito K, Takada Y, Uemoto S. Selective hemi-portocaval shunt based on portal vein pressure for small-for-size graft in adult living donor liver transplantation. Am J Transplant. 2008;8(4):847–53. doi:10.1111/j.1600-6143.2007.02144.x.
64. Taniguchi M, Shimamura T, Suzuki T, Yamashita K, Oura T, Watanabe M, et al. Transient portacaval shunt for a small-for-size graft in living donor liver transplantation. Liver Transplant. 2007;13(6):932–4. doi:10.1002/lt.21080.
65. Botha JF, Campos BD, Johanning J, Mercer D, Grant W, Langnas A. Endovascular closure of a hemiportocaval shunt after small-for-size adult-to-adult left lobe living donor liver transplantation. Liver Transplant. 2009;15(12):1671–5. doi:10.1002/lt.21944.
66. Hessheimer AJ, Fondevila C, Taura P, Munoz J, Sanchez O, Fuster J, et al. Decompression of the portal bed and twice-baseline portal inflow are necessary for the functional recovery of a "small-for-size" graft. Ann Surg. 2011;253(6):1201–10. doi:10.1097/SLA.0b013e3181ffb2d7.
67. Xiao L, Li F, Wei B, Li B, Tang CW. Small-for-size syndrome after living donor liver transplantation: successful treatment with a transjugular intrahepatic portosystemic shunt. Liver Transplant. 2012;18(9):1118–20. doi:10.1002/lt.23457.
68. Sato Y, Oya H, Yamamoto S, Kobayashi T, Hara Y, Kokai H, et al. Method for spontaneous constriction and closure of portocaval shunt using a ligamentum teres hepatis in small-for-size graft liver transplantation. Transplantation. 2010;90(11):1200–3. doi:10.1097/TP.0b013e3181fa93e0.
69. Botha JF, Langnas AN, Campos BD, Grant WJ, Freise CE, Ascher NL, et al. Left lobe adult-to-adult living donor liver transplantation: small grafts and hemiportocaval shunts in the prevention of small-for-size syndrome. Liver Transplant. 2010;16(5):649–57. doi:10.1002/lt.22043.
70. Umeda Y, Yagi T, Sadamori H, Matsukawa H, Matsuda H, Shinoura S, et al. Effects of prophylactic splenic artery modulation on portal overperfusion and liver regeneration in small-for-size graft. Transplantation. 2008;86(5):673–80. doi:10.1097/TP.0b013e318181e02d.
71. Gruttadauria S, Mandala L, Miraglia R, Caruso S, Minervini MI, Biondo D, et al. Successful treatment of small-for-size syndrome in adult-to-adult living-related liver transplantation: single center series. Clin Transplant. 2007;21(6):761–6. doi:10.1111/j.1399-0012.2007.00735.x.
72. Humar A, Beissel J, Crotteau S, Cohen M, Lake J, Payne WD. Delayed splenic artery occlusion for treatment of established small-for-size syndrome after partial liver transplantation. Liver Transplant. 2009;15(2):163–8. doi:10.1002/lt.21636.
73. Ozden I, Kara M, Pinarbasi B, Salmaslioglu A, Yavru A, Kaymakoglu S, et al. Somatostatin and propranolol to treat small-for-size syndrome that occurred despite splenic artery ligation. Exp Clin Transplant. 2007;5(2):686–9.
74. Ren YS, Qian NS, Tang Y, Liao YH, Liu WH, Raut V, et al. Beneficial effects of splenectomy on liver regeneration in a rat model of massive hepatectomy. Hepatobiliary Pancreatic Dis Int. 2012;11(1):60–5.
75. Kishi Y, Sugawara Y, Akamatsu N, Kaneko J, Tamura S, Kokudo N, et al. Splenectomy and preemptive interferon therapy for hepatitis C patients after living-donor liver transplantation. Clin Transplant. 2005;19(6):769–72. doi:10.1111/j.1399-0012.2005.00419.x.
76. Ishizaki Y, Kawasaki S, Sugo H, Yoshimoto J, Fujiwara N, Imamura H. Left lobe adult-to-adult living donor liver transplantation: should portal inflow modulation be added? Liver Transplant. 2012;18(3):305–14. doi:10.1002/lt.22440.
77. Konishi N, Ishizaki Y, Sugo H, Yoshimoto J, Miwa K, Kawasaki S. Impact of a left-lobe graft without modulation of portal flow in adult-to-adult living donor liver transplantation. Am J Transplant. 2008;8(1):170–4. doi:10.1111/j.1600-6143.2007.02037.x.
78. Samimi F, Irish WD, Eghtesad B, Demetris AJ, Starzl TE, Fung JJ. Role of splenectomy in human liver transplantation under modern-day immunosuppression. Dig Dis Sci. 1998;43(9):1931–7.
79. Bogetti D, Panaro F, Jarzembowski T, Sankary H, Benedetti E, Testa G. Hepatic venous outflow reconstruction in adult living donor liver transplants without portal hypertension. Clin Transplant. 2004;18(2):222–6. doi:10.1046/j.1399-0012.2003.00146.x.
80. Suehiro T, Shimada M, Kishikawa K, Shimura T, Soejima Y, Yoshizumi T, et al. Impact of graft hepatic vein inferior vena cava reconstruction with graft venoplasty and inferior vena cava cavoplasty in living donor adult liver transplantation using a left lobe graft. Transplantation. 2005;80(7):964–8.
81. Makuuchi M, Sugawara Y. Living-donor liver transplantation using the left liver, with special reference to vein reconstruction.

Transplantation. 2003;75(3 Suppl):S23–4. doi:10.1097/01.TP.0000046617.21019.17.
82. Yamauchi Y, Noritomi T, Yamashita Y, Mikami K, Hoshino S, Shinohara T, et al. Single orifice vein reconstruction in left liver plus caudate lobe graft. Hepatogastroenterology. 2010;57(101):813–8.
83. Urahashi T, Katsuragawa H, Yamamoto M, Ihara Y, Sanada Y, Wakiya T, et al. Use of 3-dimensional computed hepatic venous visualization for graft outflow venoplasty in adult left living-donor liver transplant. Exp Clin Transplant. 2012;10(4):350–5.
84. Onoe T, Tanaka Y, Ide K, Ishiyama K, Oshita A, Kobayashi T, et al. Attenuation of portal hypertension by continuous portal infusion of PGE1 and immunologic impact in adult-to-adult living-donor liver transplantation. Transplantation. 2013;95(12):1521–7. doi:10.1097/TP.0b013e31829150a4.
85. Morioka D, Kubota T, Sekido H, Matsuo K, Saito S, Ichikawa Y, et al. Prostaglandin E1 improved the function of transplanted fatty liver in a rat reduced-size-liver transplantation model under conditions of permissible cold preservation. Liver Transplant. 2003;9(1):79–86. doi:10.1053/jlts.2003.36845.
86. Man K, Lee TK, Liang TB, Lo CM, Fung PC, Tsui SH, et al. FK 409 ameliorates small-for-size liver graft injury by attenuation of portal hypertension and down-regulation of Egr-1 pathway. Ann Surg. 2004;240(1):159–68.
87. Palmes D, Budny TB, Stratmann U, Herbst H, Spiegel HU. Endothelin-A receptor antagonist reduces microcirculatory disturbances and transplant dysfunction after partial liver transplantation. Liver Transplant. 2003;9(9):929–39. doi:10.1053/jlts.2003.50191.
88. Tang LM, Wang YP, Wang K, Pu LY, Zhang F, Li XC, et al. Protective effect of adenosine A2A receptor activation in small-for-size liver transplantation. Transplant Int. 2007;20(1):93–101. doi:10.1111/j.1432-2277.2006.00394.x.
89. Yamanaka K, Hatano E, Iguchi K, Yamamoto G, Sato M, Toriguchi K, et al. Effect of olprinone on liver microstructure in rat partial liver transplantation. J Surg Res. 2013;183(1):391–6. doi:10.1016/j.jss.2012.11.033.
90. Yang ZF, Tsui TY, Ho DW, Tang TC, Fan ST. Heme oxygenase-1 potentiates the survival of small-for-size liver graft. Liver Transplant. 2004;10(6):784–93. doi:10.1002/lt.20142.
91. Cui YY, Qian JM, Yao AH, Ma ZY, Qian XF, Zha XM, et al. SOD mimetic improves the function, growth, and survival of small-size liver grafts after transplantation in rats. Transplantation. 2012;94(7):687–94. doi:10.1097/TP.0b013e3182633478.
92. Tian Y, Graf R, El-Badry AM, Lesurtel M, Furrer K, Moritz W, et al. Activation of serotonin receptor-2B rescues small-for-size liver graft failure in mice. Hepatology. 2011;53(1):253–62. doi:10.1002/hep.23960.
93. Guo L, Haga S, Enosawa S, Naruse K, Harihara Y, Sugawara Y, et al. Improved hepatic regeneration with reduced injury by redox factor-1 in a rat small-sized liver transplant model. Am J Transplant. 2004;4(6):879–87. doi:10.1111/j.1600-6143.2004.00444.x.
94. Xu MQ, Suo YP, Gong JP, Zhang MM, Yan LN. Augmented regeneration of partial liver allograft induced by nuclear factor-kappaB decoy oligodeoxynucleotides-modified dendritic cells. World J Gastroenterol. 2004;10(4):573–8.
95. Yagi S, Doorschodt BM, Afify M, Klinge U, Kobayashi E, Uemoto S, et al. Improved preservation and microcirculation with POLYSOL after partial liver transplantation in rats. J Surg Res. 2011;167(2):e375–83. doi:10.1016/j.jss.2010.12.040.

ELSEVIER

Impact of Machine Perfusion Preservation of Liver Grafts From Donation After Cardiac Death

N. Matsuno[a,b,c,*], K. Uchida[c], and H. Furukawa[c]

[a]Department of Innovative Surgery and Transplantation, National Research Institute, National Center for Child Health and Development, Tokyo, Japan; [b]Mechanical Engineering, Tokyo Metropolitan University, Tokyo, Japan; and the [c]Department of Surgery, Asahikawa Medical University, Hokkaido, Japan

ABSTRACT

Because of the critical shortage of deceased donor grafts, using a donation after cardiac death (DCD) donor is an important resource. However, the ischemic damage of those DCD grafts jeopardizes organ viability during cold storage. Maintaining organ viability after donation until transplantation is important for optimal graft function and survival. This review describes the effective preservation in transplantation for DCD livers. Concepts and development of machine perfusion for DCD liver grafts to reduce ischemia/reperfusion injury are discussed. Despite the fact that hypothermic machine perfusion might be superior to static cold preservation, DCD livers are exposed to hypothermia-induced damage. Recently, some groups introduced the beneficial effects of normothermic or subnormothermic machine perfusion in DCD liver preservation and transplantation.

THE SHORTAGE of donors for transplantation is a universal problem. The wait list for organs has continued to grow. However, the use of marginal donors is a promising way to increase the supply. In particular, use of organs from non–heart-beating donors (NHBD) and donation after cardiac death (DCD) are gaining importance as potential sources of vital organs for clinical transplantation. The two approaches to preservation before transplantation are simple cold storage (SCS) and machine perfusion (MP). The simplicity, lower cost, and need for transport make cold storage the method of choice for the majority of transplantation centers. However, the major principle of simple hypothermic liver preservation is the reduction of metabolic activity. Although MP using hypothermia may have a theoretical advantage in providing metabolic support and oxygenation, its use has not become widespread in clinical practice. Recently, the short- and long-term function of kidneys procured from DCDs by means of normothermic recirculation were reported [1]. The principle of normothermic and subnormothermic perfusion is to recreate the physiological environment by providing the essential substrates for cellular metabolism, oxygenation, and nutrition. In this review, based on the historical background of transplantation from DCD, clinical donor criteria for DCD livers and the progress of MP for DCD livers in cold storage are introduced. Finally, the method of rewarming preservation for DCD liver transplantation is introduced as a challenge using a new MP system.

HISTORICAL BACKGROUND FOR LIVER TRANSPLANTATION FROM DCD DONORS

In March 1995, an international workshop for NHBD was held in Maastricht, Netherlands. DCDs had been classified as the Maastricht classification [2]. Categories 1, 2, and 4 include uncontrolled DCDs, and category 3 includes controlled DCDs. DCDs have come to represent the fastest growing proportion of the donor pool. In some United Network for Organ Sharing (UNOS) regions with limited standard criteria for donors, DCDs comprised up to 16% to 21% of the total donor pool [3]. After successful use of DCD kidney grafts for clinical transplantation, interest has moved toward using extrarenal organs such as the liver, pancreas, and lungs [4]. However, in the early phase, liver transplantations from DCDs did not always show favorable post-transplantation results. The development of ischemic biliary stricture is a major source of morbidity after DCD liver transplantation.

Retransplantation is also associated with a significantly higher mortality risk. The difficulty with using DCD livers has been considered to be that, although the incidence of

*Address correspondence to Naoto Matsuno, MD, PhD, Department of Innovative and Transplant Surgery, National Center for Child Health and Development, 2-10-1 Okura, Setagaya, Tokyo, 157-8535, Japan. E-mail: mtnnot@yahoo.co.jp

0041-1345/14/$-see front matter
http://dx.doi.org/10.1016/j.transproceed.2013.11.135

delayed graft function (DGF) in the kidneys is high, it can be treated with hemodialysis until the kidneys recover. In contrast, DGF in the liver often requires retransplantation as rescue therapy. For this reason, there has been great caution in using DCD liver grafts. Recently, the incidences of primary non-function (PNF) and severe DGF have been remarkably reduced due to the use of selected controlled DCD livers, better selection criteria for advanced preservation technologies, and shortened warm and cold ischemic times. However, this strategy does not always lead to a significant increase in donor numbers. Further studies are needed to identify clinical strategies, such as improving organ preservation, and policies to reduce incidences and improve the outcome of PNF and ischemic cholangiopathy in recipients who have DCD liver grafts.

MP Preservation of Liver Grafts

The introduction of kidney perfusion preservation in clinical practice started in the late 1960s. Folkert O.Belzer had already been working on the continuous hypothermic isolated perfusion and auto-kidney transplantation with blood [5] and cryoprecipitated plasma [6]. The hypothermic MP (HMP) of the first human kidney became a clinical reality soon thereafter; a patient received a kidney that had been preserved for 17 hours using this preservation circuit, and had acceptable function post-transplantation [6]. In the 1970s, HMP was used by transplantation centers mainly in the United States and Europe to preserve and transport kidneys. Consequently, different perfusion machines were also developed and used clinically for kidney preservation. Currently, there are three commercially available renal perfusion devices: the RM3 from Waters Medical Systems (Rochester, MN, USA) (Fig 1A), the LifePort from Organ Recovery Systems (Fig 1B), and the Kidney Assist by Organ Assist b.v. (Groningen, The Netherlands) (Figs 1C,D). However, in 1980, the development of the University of Wisconsin (UW) solution produced by the same UW group allowed surgeons to preserve kidneys for much longer time, up to 72 hours, by simple cold storage [7]. The development of the UW solution provided an alternative to MP, and most centers abandoned the clinical use of MP. During the last few decades, the success of kidney transplantation as the treatment of choice for end-stage renal failure has led to an increasing shortage of suitable organs. This shortage has forced the transplantation community to (re-) consider the transplantation of organs from marginal donors, such as older donors, hemodynamically unstable donors, and NHBD donors. Thereafter, the MP of kidneys from these marginal donors regained worldwide interest.

The international multicenter trial for HMP during kidney transplantation is a well-designed prospective randomized trial of paired kidneys [8], one preserved with SCS and one with MP. The study examined 672 renal transplantations performed in Europe. MP significantly reduced the risk of DGF, as well as significantly improving the rate of the decrease in the serum creatinine level. The number of use of HMP before kidney transplantation is now increased. Regarding liver preservation, Guarrera et al [9] showed the

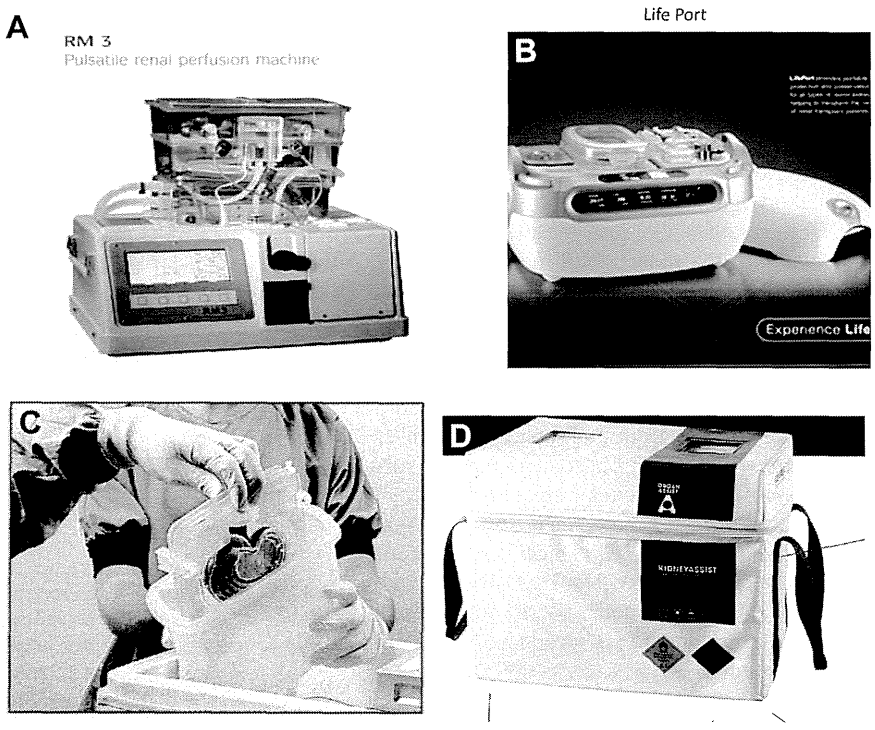

Fig 1. **(A)** RM-3 by Waters Medical System (Rochester, MN, USA). **(B)** LifePort Kidney Transporter by Organ Recovery System Des Plaines. **(C, D)** Kidney Assist by Organ Assist b.v. (Groningen, The Netherlands).

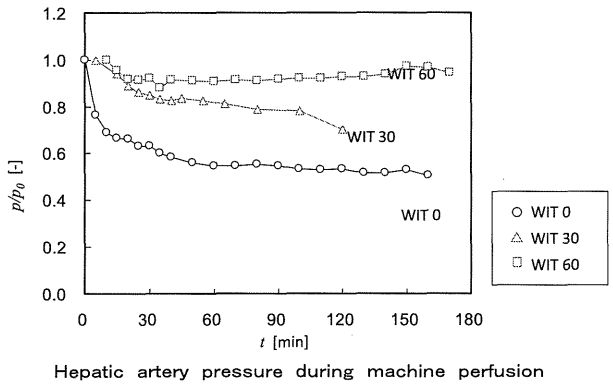

Fig 2. Changes of pressure in hepatic artery during machine perfusion.

outcomes of liver transplantation after 12 hours of HMP or with SCS in a miniature swine model using a new preservation solution, the Vasosolution, which uses a modified Belzer's MP solution. The serum aspartate aminotransferase (AST) and total bilirubin levels were similar in the HMP and SCS groups, indicating that HMP can be used successfully. Later, the Guarrera group reported successful use in human livers. The outcomes of liver transplantation were reported to be satisfactory compared with simple cold storage [10].

Pretransplantation viability testing for a DCD graft is particularly important. An advantage of using MP preservation is that it enables the performance of viability tests on the grafts while they are stored. Preservation by machine enables the physician to judge the acceptability of the graft by registering the flow and pressure characteristics and analyzing the enzymes in the perfusate. Developing a system of MP to establish viability assessments of the liver has not been easy due to the unique blood supply of liver grafts. Predicting viability by evaluating flow in the portal system is not possible because the portal flow is wide ranged and the systems used have found it difficult to generate portal pressure that shows efficient portal flow in the hypothermic stage. Even tissue and vascular resistance, which provide important information in kidney preservation, are particularly low due to easy destruction in the liver. The effluent AST and lactate dehydrogenase (LDH) levels collected in preservation solution have been reported to be useful and predictable biomarkers in previous reports [11–13]. Recently, Obara et al developed a novel liver perfusion system and found that the degree of decreasing hepatic arterial pressure is significantly correlated with the length of warm ischemic time (Fig 2) and the levels of liver enzymes (AST, LDH) in cold perfusate during continuous preservation [14] (Fig 2).

Challenge in DCD Liver Grafts Using MP

Despite successful MP for DCD kidney grafts, DCD liver transplantation has been challenging. There are important limitations of basic research using small animals because of the difficulties associated with assessment of the hepatic artery flow. In large-animal and clinical studies, successful transplantation was achieved by Brettschneider et al after 24 hours of MP in a canine model [15]. Starzl et al preserved the first 11 human livers up to 7.5 hours by the same method [16]. However, the use of fresh diluted blood is inconvenient in the clinical setting. Low-pressure HMP was applied via the hepatic artery in porcine livers for 2 hours before transplantation and compared to similar grafts stored in cold Euro-Collins solution for the same period. Both the LDH and AST levels were consistently lower in the HMP group compared with the SCS group [17]. A new preservation solution, Polysol, was developed for MP by the Amsterdam group in 2005. Polysol solution contains many vitamins and a protein-like, enriched tissue culture medium for functional recovery during preservation, which is expensive [18,19]. As for DCD liver grafts in large animals, most groups agree that 30 minutes of warm ischemic time (WIT) plus 4 to 5 hours of cold preservation results in primary loss of function in the pig liver [20,21]. Dutkowski used a large animal model to test whether short-term hypothermic oxygenated perfusion (HOPE) – treated DCD livers could experience the same benefits as those noted in the previous report using a rat model. The porcine DCD liver with 60 minutes of WIT preserved with SCS for 6 hours could be rescued by a 1 hour short-term HOPE treatment [22]. Lower values of AST and LDH after reperfusion, and a higher survival rate up to 30 hours in the HOPE group were shown. We developed a new preservation machine with a temperature-controlled system (NES) (Fig 3A). We reported beneficial functional recovery in the HMP group after 30 minutes of WIT plus 4

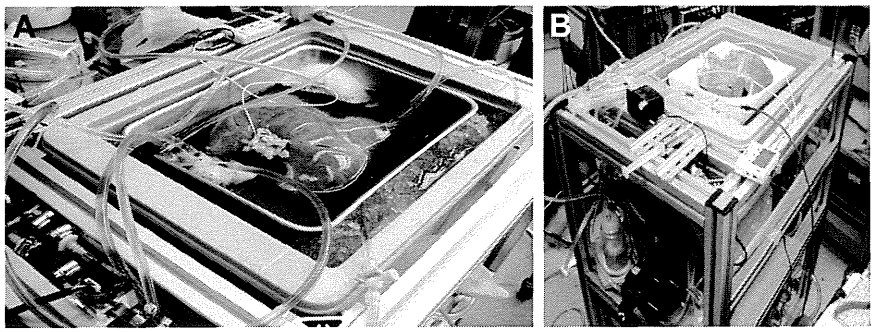

Fig 3. (A, B) Liver Perfusion System (NES).

to 5 hours of total ischemic time compared to the SCS-only group in a porcine liver transplantation model [23]. On the other hand, the concept for DCD graft has been changed and reported in recent years. Experimental studies have shown that even brief periods of cold preservation will cause injury to hepatocytes, Kupffer cells, and endothelial cells in DCD livers, even those later recirculated under normothermia. The use of normothermic extracorporeal membrane oxygenated (NECMO) perfusion is based on experimental studies which have shown that the recirculation of oxygenated blood at 37°C improves the cellular energy load, reduces tissue injury, and improves the post-transplantation graft function in livers damaged by the period of warm ischemia caused by cardiac arrest [24,25]. In 2002, the Hospital Clinic in Barcelona developed a clinical protocol to resuscitate organs from donors and to maintain viability for transplantation [26]. The protocol includes cannulation of the femoral vessels to establish an NECMO circuit. NECMO is used to reperfuse and oxygenate abdominal organs after cardiac arrest while the potential DCD is evaluated and consent for organ donation is obtained. In 2007, the first 10 human liver transplantations were performed with uncontrolled DCDs in which the donor was maintained with NECMO before organ retrieval. Ten DCD livers were transplanted with only 1 graft lost to PNF and 1 to hepatic artery thrombosis. In March 2013, two cases of human warm liver perfusion were successfully transplanted in Kings College Hospital group. The great advantage of normothermic preservation, including the use of NECMO, is the ability to overcome the disadvantaged aspects of hypothermic cellular physiology [27]. However, the use of blood-based perfusates may increase the risk of microvascular failure and sinusoidal plugging and bacterial growth. Normothermic preservation requires full metabolic support with a large machine. Additionally, any equipment failures result in unexpected warm ischemic injury. Therefore, achieving normothermic liver preservation remains troublesome and expensive. The reality of clinical organ retrieval might require a period of cold preservation due to transport between institutions. Some studies have investigated the perfusion temperature. For example, subnormothermic MP performed at 20°C resulted in reduced vasoconstriction, as well as lower metabolic requirements in DCD [28] and steatotic [29] rat models. Shigeta et al successfully transplanted porcine livers with 60 minutes of WIT plus 4 hours of total ischemic time by rewarming preservation from 4°C to 22°C using MP [30]. Development of liver perfusion system in the world is shown in Figure 4.

CONCLUSION

Traditional methods of hypothermic preservation based on both static and machine storage may not be best for DCD liver grafts because liver organs from DCDs have already suffered severe tissue damage secondary to hypoxia and hypoperfusion before the initial period of warm ischemia. Additional cold storage damage to the organ caused by hypothermic conditions may limit the ability to improve cellular function because metabolic activity is decreased in the cold storage. Ideally, these livers will be continuously perfused ex vivo with warm or subnormothermic oxygenated preservation solution. Rewarming preservation during perfusion may become practically available and useful.

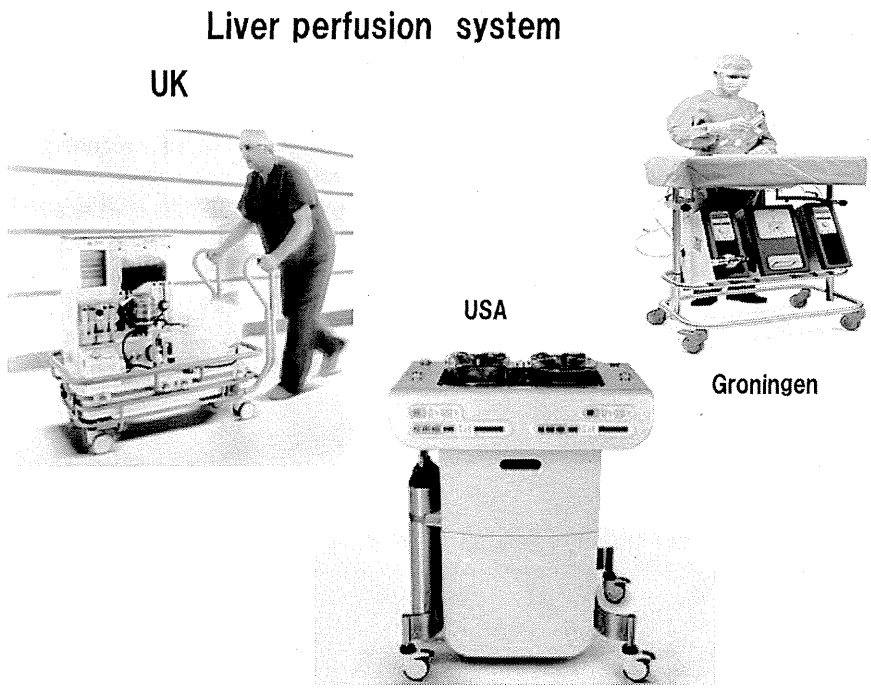

Fig 4. Development of liver perfusion system.

REFERENCES

[1] Valero R, Cabrer C, Oppenheimer F, et al. Normothermic recirculation reduces primary graft dysfunction of kidneys obtained from non–heart-beating donors. Transpl Int 2000;13(4):303–10.

[2] Kootstra G, Daemen JH, Oomen AP. Categories of non–heart-beating donors. Transplant Proc 1995;27(5):2893–4.

[3] United Network for Organ Sharing. Available at: http://www.unos.org/. Accessed February 15, 2010.

[4] D'Alessandro AM, Hoffmann RM, Knechtle SJ, et al. Successful extrarenal transplantation from non–heart-beating donors. Transplantation 1995;59(7):977–82.

[5] Belzer FO, Park HY, Vetto RM. Factors influencing renal blood flow during isolated perfusion. Surg Forum 1964;15:222–4.

[6] Belzer FO, Ashby BS, Gulyassy PF, et al. Successful seventeen-hour preservation and transplantation of human-cadaver kidney. N Engl J Med 1968;278(11):608–10.

[7] Hoffmann RM, Southard JH, Belzer FO. The use of oncotic support agents in perfusion preservation. In: Pegg DE, Jacobsen IA, Halasz NA, editors. Organ Preservation, Basic and Applied Aspects. Lancaster: MTP Press; 1982. pp. 261–5.

[8] Moers C, Smits JM, Maathuis MH, et al. Machine perfusion or cold storage in deceased-donor kidney transplantation. N Engl J Med 2009;360(1):7–19.

[9] Guarrera JV, Esteves J, Boykin J, et al. Hypothermic machine perfusion of liver grafts for transplantation: technical development in human discard and miniature swine models. Transplant Proc 2005;37(1):323–5.

[10] Guarrera JV, Henry SD, Samstein B, et al. Hypothermic machine preservation in human liver transplantation: the first clinical series. Am J Transplant 2010;10(2):372–81.

[11] Bessems M, Doorschodt BM, van Marle J, et al. Improved machine perfusion preservation of the non–heart-beating donor rat liver using Polysol: a new machine perfusion preservation solution. Liver Transpl 2005;11(11):1379–88.

[12] van der Plaats A, Maathuis MHT, Hart NA, et al. The Groningen hypothermic liver perfusion pump: functional evaluation of a new machine perfusion system. Ann Biomed Eng 2006;34(12):1924–34.

[13] Obara H, Matsuno N, Shigeta T, et al. Temperature controlled machine perfusion system for liver. Transplant Proc 2013;45(5):1690–2.

[14] Obara H, Matsuno N, Enosawa S, et al. Pretransplant screening and evaluation of liver graft viability using machine perfusion preservation in porcine transplantation. Tranplant Proc 2012;44(4):959–61.

[15] Brettschneider L, Daloze PM, Huquet C, et al. Successful orthotopic transplantation of liver homografts after 8 to 25 hours preservation. Surg Forum 1967;18:376–8.

[16] Starzl TE. Experience in hepatic transplantation. Philadelphia, PA: W.B. Saunders; 1969. pp. 365.

[17] Uchiyama M, Kozaki K, Matsuno N, et al. Usefulness of preservation method by machine perfusion and pentoxifylline on the liver transplantation from non–heart beating donor. J Tokyo Med U 2000;58(6):743–56.

[18] Doorschodt BM, Bessems M, van Vliet AK, et al. The first disposable perfusion preservation system for kidney and liver grafts. Ann Transplant 2004;9(2):40–1.

[19] Bessems M, Doorschodt BM, van Vliet AK, et al. Improved rat liver preservation by hypothermic continuous machine perfusion using polysol, a new, enriched preservation solution. Liver Transpl 2005;11(5):539–46.

[20] Monbaliu D, Crabbé T, Roskams T, et al. Livers from non–heart-beating donors tolerate short periods of warm ischemia. Transplantation 2005;79(9):1226–30.

[21] Takada Y, Taniguchi H, Fukunaga K, et al. Hepatic allograft procurement from non–heart-beating donors: limits of warm ischemia in porcine liver transplantation. Transplantation 1997;63(3):369–73.

[22] de Rougemont O, Breitenstein S, Leskosek B, et al. One hour hypothermic oxygenated perfusion (HOPE) protects nonviable liver allografts donated after cardiac death. Ann Surg 2009;250(5):674–83.

[23] Shigeta T, Matsuno N, Obara H, et al. Functional recovery of donation after cardiac death liver graft by continuous machine perfusion preservation in pigs. Transplant Proc 2012;44(4):946–7.

[24] García-Valdecasas JC, Tabet J, Valero R, et al. Liver conditioning after cardiac arrest: the use of normothermic recirculation in an experimental animal model. Transpl Int 1998;11(6):424–32.

[25] Net M, Valero R, Almenara R, et al. The effect of normothermic recirculation is mediated by ischemic preconditioning in NHBD liver transplantation. Am J Tranplant 2005;5(10):2385–92.

[26] Fondevila C, Hessheimer AJ, Ruiz A, et al. Liver transplant using donors after unexpected cardiac death: novel preservation protocol and acceptance criteria. Am J Transplant 2007;7(7):1849–55.

[27] Fondevila C, Hessheimer AJ, Maathuis MH, et al. Superior preservation of DCD livers with continuous normothermic perfusion. Ann Surg 2011;254(6):1000–7.

[28] Dutkowski P, Furrer K, Tian Y, et al. Novel short-term hyptohermic oxygenated perfusion (HOPE) system prevents injury in rat liver graft from non-heart beating donor. Ann Surg 2006;244(6):968–76.

[29] Olschewski P, Gass P, Ariyakhagorn V, et al. The influence of storage temperature during machine perfusion on preservation quality of marginal donor livers. Cryobiology 2010;60(3):337–43.

[30] Shigeta T, Matsuno N, Obara H, et al. Impact of rewarming preservation by continuous machine perfusion: improved post-transplant recovery in pigs. Transplant Proc 2013;45(5):1684–9.

ELSEVIER

Establishment of Educational Program for Multiorgan Procurement From Deceased Donors

M. Taniguchi, H. Furukawa, T. Kawai, H. Morikawa, K. Morozumi, M. Goto, T. Kondo, A. Aikawa, T. Ito, S. Takahara, M. Nio, N. Kokudo, S. Uemoto, N. Fukushima, K. Yoshida, T. Kenmochi, H. Date, M. Ono, S. Eguchi, T. Shimamura, K. Mizuta, T. Yoshizumi, and T. Ueno

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

From the Asahikawa Medical University, Asahikawa (M.T., H.F.); Waseda University, Tokyo (T. Kawai); Aoyama Gakuin University, Tokyo (H.M.); Japanese Red Cross Nagoya Daini Hospital, Nagoya (K. Morozumi); Fukushima Medical University, Fukushima (M.G.); Tohoku University, Sendai (T. Kondo, M.N.); Toho University, Tokyo (A.A.); Osaka University, Suita (T.I., S.T., N.F., T.U.); Tokyo University, Tokyo (N.K., M.O.); Kyoto University, Kyoto (S.U., H.D.); Kitasato University, Sagamihara (K.Y.); Fujita Health University, Toyoake (T. Kenmochi); Nagasaki University, Nagasaki (S.E.); Hokkaido University, Sapporo (T.S.); Jichi Medical University, Shimotsuke (K. Mizuta); and Kyusyu University, Fukuoka (T.Y.), Japan.

The work was supported by grants-in-aid from the Ministry of Health, Labour and Welfare, Japan.

Address reprint requests to Hiroyuki Furukawa, MD, Asahikawa Medical University, Department of Gastroenterologic and General Surgery, 2-Jyo 1-Chome 1-1, Midorigaoka-Higashi, Asahikawa, Hokkaido, Japan. E-mail: f-hiro@asahikawa-med.ac.jp

0041-1345/14/$–see front matter
http://dx.doi.org/10.1016/j.transproceed.2014.02.002

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.

ACKNOWLEDGMENT

The authors express sincere gratitude to all of the 22 deceased donor liver transplantation programs participating in this survey: Hokkaido University, Tohoku University, Iwate Medical University, Tokyo University, Jichi Medical University, National Center for Child Health and Development, Keio University, Juntendo University, Shinshu University, Niigata University, Nagoya University, Mie University, Kanazawa University, Kyoto University, Kyoto Prefecture University of Medicine, Osaka University, Kobe University, Okayama University, Hiroshima University, Kyusyu University, Nagasaki University, and Kumamoto University.

REFERENCE

[1] Furukawa H, Taniguchi M, Fujiyoshi M, Ota M; and the Japanese Study Group of Liver Transplantation. Experience using extended criteria donors in first 100 cases of deceased donor liver transplantation in Japan. Transplant Proc 2012;44:373.

Cyst Infection of Intraductal Papillary Mucinous Neoplasms of the Pancreas: Management of a Rare Complication

Report of 2 Cases

Kenji Watanabe, MD, Hidenori Karasaki, MD, PhD,† Yusuke Mizukami, MD, PhD,‡ Toru Kawamoto, MD, PhD,§ Toru Kono, MD, PhD,|| Koji Imai, MD, PhD,* Takahiro Einama, MD, PhD,* Masahiko Taniguchi, MD, PhD,* Yutaka Kohgo, MD, PhD,§ and Hiroyuki Furukawa, MD, PhD**

Abstract: The purpose of this study was to describe the cyst infection of intraductal papillary mucinous neoplasm in 2 patients. The patients were 62- and 74-year-old men. The initial symptom was acute febrile abdominal pain. Laboratory tests revealed severe infection (C-reactive protein concentrations were 23.3 μg/mL in patient 1 and 22.3 μg/mL in patient 2) and multilocular cystic masses (the diameters were 70 mm in patient 1 and 50 mm in patient 2) at the pancreatic head that involved peripancreatic vessels were demonstrated by computed tomography. Laboratory and radiographic findings were markedly improved by endoscopic transpapillary drainage. The enteric bacteria were detected in the drainage specimens. Curative resection was achieved, and histological findings indicated a carcinoma in situ in patient 1 and an invasive carcinoma in patient 2. Neither hyperamylasemia nor histological fat necrosis, frequently observed in acute pancreatitis, was evident. Both patients were free from recurrence after surgery (17 months in patient 1, and 18 months in patient 2). Cyst infection is an unknown complication of intraductal papillary mucinous neoplasm. Transpapillary drainage is highly recommended as an initial intervention. It is difficult to distinguish between cyst infection and unresectable invasive carcinoma with imaging modalities; however, surgical intervention after drainage may contribute to long-term survival.

Key Words: intraductal papillary mucinous neoplasms, cyst infection, transpapillary drainage

(*Pancreas* 2014;43: 478–481)

Intraductal papillary mucinous neoplasm (IPMN) of the pancreas is a common pancreatic tumor that is characterized by the intraductal and papillary proliferation of neoplastic cells and the production of thick fluid.[1] Since it was originally described in the 1980s by Ohashi et al,[2] a large number of studies have been performed to establish the etiology of this tumor. Intraductal papillary mucinous neoplasms are classified as main-duct or branch-duct types depending on the location of the lesion.[3] They are also subdivided into 4 types (gastric, intestinal, pancreaticobiliary, and oncocytic) based on morphological features.[4] Although a number of studies have investigated the use of imaging modalities or cytogenetic analysis of tissue and fluid samples obtained by endoscopy to estimate tumor grade, IPMN staging is still subject to debate.[5,6] In general, surgical intervention is highly recommended for patients with main duct tumors or large branch-duct tumors with mural nodules.[7] In addition, patients who have IPMN-related symptoms are generally considered to be candidates for surgical resection.[8] Acute pancreatitis (AP), caused by large amounts of mucin, has been recognized as a major complication of IPMN, and the incidence of AP in the largest surgical series published to date varied from 12% to 67%.[9] Sendai guidelines recommend surgical resection in patients with branch-duct IPMN and clinical symptoms, including AP.[3] In contrast with the relatively high frequency of AP coexistent with IPMNs, reports of cyst infection associated with IPMN are rare. We report our experience with 2 patients with IPMN who developed sepsis due to cyst infection, which is a rare but notable complication of IPMN. Herein, we discuss the diagnosis, initial treatment, and management strategy for IPMN associated with cyst infection, which may represent an unknown complication of IPMN.

PATIENT 1

A 62-year-old man was admitted to a local clinic complaining of epigastralgia with fever. He was treated by administration of antibiotics without relief of symptoms. The patient was then referred to our hospital for further intervention. He had been abusing alcohol (360 mL of distilled spirits per day) for 40 years and had diabetes mellitus, hypertension, and benign prostatic hypertrophy. There was no history of AP. Blood tests revealed a marked inflammatory response: 18,660 white blood cells/μL and 23.3 μg/mL C-reactive protein (CRP). All of the tumor markers that we examined were within reference range. Serum pancreatic amylase values were within normal limits, but elastase 1 was elevated to 640 ng/dL. A computed tomography (CT) scan revealed a multilocular cystic tumor 70 mm in diameter at the head and the uncinate process of the pancreas. The tumor involved peripancreatic vessels, including the celiac artery, the superior mesenteric artery, and the portal vein (PV) (Figs. 1A, B, and D). Transpapillary nasopancreatic drainage tube, 7F in diameter, was inserted to cyst immediately after admission to our hospital. Cannulation was not difficult, because the orifice of the duodenal papilla was markedly dilated by copious amounts of mucin (Fig. 1G). The patient defervesced 3 days after drainage. The amount of drainage fluid was 170 mL at day 1 and decreased to 32 mL at day 3 after procedure. The drainage tube was removed at 9 days after drainage. *Enterococcus faecalis* and *Escherichia coli* were detected in the pus discharge. Cytological examination of the drained fluid revealed mucin-producing papillary clusters with mild atypia and positive immunoreactivity for MUC2 and NUC5AC. Both laboratory and imaging findings

From the *Division of Gastroenterological and General Surgery, Department of Surgery, Asahikawa Medical University; †Department of Surgery, Social Work Association Furano Hospital; ‡Center for Clinical and Biomedical Research, Sapporo Higashi Tokushukai Hospital; §Division of Gastroenterology and Hematology/Oncology, Department of Medicine, Asahikawa Medical University; and ||Advanced Surgery Center, Sapporo Higashi Tokushukai Hospital, Hokkaido, Japan.

Received for publication March 9, 2013; accepted August 9, 2013.

Reprints: Hidenori Karasaki, MD, PhD, Department of Surgery, Social Work Association Furano Hospital, 1-30 Sumiyoshityo, Furano, Hokkaido 076-8765, Japan (e-mail: hide.karasaki@gmail.com).

The authors declare no conflict of interest.