Small for size syndrome following living donor and split liver transplantation

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Abstract
The field of liver transplantation is limited by the availability of donor organs. The use of living donor and split cadaveric grafts is one potential method of expanding the donor pool. However, primary graft dysfunction can result from the use of partial livers despite the absence of other causes such as vascular obstruction or sepsis. This increasingly recognised phenomenon is termed “Small-for-size syndrome” (SFSS). Studies in animal models and humans have suggested portal hyperperfusion of the graft combined with poor venous outflow and reduced arterial flow might cause sinusoidal congestion and endothelial dysfunction. Graft related factors such as graft to recipient body weight ratio < 0.8, impaired venous outflow, steatosis > 30% and prolonged warm/cold ischemia time are positively predictive of SFSS. Donor related factors include deranged liver function tests and prolonged intensive care unit stay greater than five days. Child-Pugh grade C recipients are at relatively greater risk of developing SFSS. Surgical approaches to prevent SFSS fall into two categories: those targeting portal hyperperfusion by reducing inflow to the graft, including splenic artery modulation and portacaval shunts; and those aiming to relieve parenchymal congestion. This review aims to examine the controversial diagnosis of SFSS, including current strategies to predict and prevent its occurrence. We will also consider whether such interventions could jeopardize the graft by compromising regeneration.

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Key words: Liver transplantation; Living donors; Hypertension; Portal; Splenic artery; Liver regeneration; Hepatic veins; Portacaval shunt; Surgical

INTRODUCTION
From the beginning, transplant surgery has always been limited by organ availability. Split cadaveric and living donor grafts have gained popularity in the past twenty years as initial technical hurdles were overcome. From 1988 to 2008 a total of 4103 split cadaveric and 3079 living donor transplantations were carried out in Europe[1] and over 75% of these have taken place in adult-to-adult cases. This practice has generated a phenomenon known as “Small-for-size-syndrome” (SFSS), where a small graft exhibits primary dysfunction. The name is misleading; the graft need not necessarily be small if it is steatotic or if the recipient has adverse risk factors such as existing portal hypertension and Child-Pugh grade C. This review explores the putative mechanism underlying SFSS, risk factors, prevention and treatments.
PATHOPHYSIOLOGY OF “SMALL-FOR-SIZE SYNDROME”

SFSS has become increasingly recognised in the last 20 years since partial liver grafts made the leap from paediatric to adult transplantation. SFSS in orthotopic liver transplantation describes a condition in which a small graft (graft to recipient weight ratio < 0.8) exhibits signs of primary graft dysfunction within the first post operative week in the absence of other diagnoses such as vascular obstruction, biliary leak, sepsis and immune rejection[13]. Coagulopathy, ascites and hyperbilirubinemia are typical manifestations. This definition derives from a survey of 20 expert partial liver transplant surgeons across the world[14]. Whilst all 20 consider SFSS to be a distinct clinical entity, opinion on its underlying pathological basis is very much divided. Most of them consider that portal hyperperfusion forms part of the syndrome but less consensus was obtained about the importance of the role played by outflow obstruction.

Portal hyperperfusion, venous congestion and arterial hypoperfusion, as well as simple insufficiency of liver mass, have all been suggested as contributory mechanisms for pathogenesis. Several case series of living donor liver transplants[15,16] have shown significant elevation of venous pressure in small grafts [graft weight to recipient body weight ratio (GWRW) < 0.8]. Differentially elevated portal venous pressure (PVP) in small grafts persisted for as long as fourteen days post operatively compared to non-SFSS grafts[17]. This is clinically significant as PVP > 20 mmHg is correlated with poorer graft survival (38% at 85%) at six months[18].

Recently, rat, mouse and porcine models have given valuable insight into SFSS under controlled conditions[19,20]. A porcine model where recipients were transplanted with 19.3%-25.3% standard liver volume showed significant increases in portal venous flow, portal pressure and vascular resistance, along with reduced arterial flow. In addition, markers of endothelial and hepatocyte injury were markedly elevated compared to the whole graft group[21]. Another porcine model using a range of liver graft sizes demonstrated typical histopathology of SFSS. Congestion, hemorrhage, sinusoidal/endothelial damage, septal edema and architectural disruption can be seen as soon as five minutes post reperfusion and persist for up to five days postoperatively in small 20%-30% grafts. These histological changes were more severe and prolonged in the smaller grafts[22]. These findings correlate with a human study showing sinusoidal endothelial disruption and focal hemorrhage dissecting into connective tissue, along with hepatic artery spasm[23]. However, regeneration rate was also markedly increased in SFSS grafts, a common theme across both human and animal studies, suggesting a degree of portal hyperperfusion may be necessary to induce liver regeneration. An important caveat of animal models in SFSS is that none have taken into account disease status in the recipient, a crucial consideration in human orthotopic liver transplants.

The role of arterial hypoperfusion in SFSS is less well studied as it is secondary to portal hyperperfusion. Low hepatic artery flow seen in post-transplant grafts was formerly thought to be related to diversion of blood through the splenic artery and was called “splenic artery steal syndrome” but is now considered to be due to a normal homeostatic mechanism termed hepatic arterial buffer response (HABR)[24]. The role of HABR is to maintain constant total blood flow to the liver and it is mediated by adenosine washout. Portal blood flow removes adenosine which has a local vasodilator effect on the arterial system[25,26]. However, in states of extreme portal hyperperfusion as seen in small-for-size grafts, an exaggerated HABR may contribute to ischemic injury[27,28]. In one porcine small-for-size model, an infusion of adenosine in 20% standard liver size grafts was able to inhibit HABR and significantly reduce graft injury as determined by histology[18].

PREDICTING SFSS

Is it possible to identify cases at greater risk of developing SFSS? Commonly cited pre-operative risk factors include GWRW < 0.8[29] or graft weight ratio less than 30%-40%, with small grafts at significantly greater risk of prolonged bilirubinemia and coagulopathy. The first study is notable as 88% of patients were pediatric recipients undergoing transplant post-Kasai procedure, not representative of the usual adult liver transplant population. However, more recent studies have suggested small graft size alone is insufficient to account for SFSS. One retrospective study of 107 patients[30] undergoing live donor (n = 76) and split cadaveric transplants (n = 31) found no significant difference in either incidence of SFSS or graft survival at one year between the GWRW < 0.8% group (n = 22) and > 0.8% (n = 85) group, although the author reported a significantly greater number of SFSS cases in the 0.8%-1.0% region. In another study on a series of 75 patients[31], no difference was observed in development of SFSS between those receiving grafts less than 40% standard liver volume (n = 26) compared to those that received more than 40% (n = 73). This discrepancy can be accounted for in several ways. Firstly, there is increasing recognition that factors such as graft steatosis, pre-existing portal hypertension, recipient Child-Pugh grade and venous congestion also contribute to SFSS. Secondly, retrospective studies may lack power to detect a significant difference as a much smaller proportion of patients receive small-for-size grafts. Thirdly, in the later studies, patients thought at greater risk of developing SFSS often receive prophylactic measures such as splenic artery ligation[31].

When small-for-size grafts are stratified by disease severity in the recipient, it has been shown that SFSS is more likely to occur in patients with Child-Pugh score B and C. One-year graft survival is also significantly lower if Child B and C patients receive grafts GWRW < 0.8% and this is in addition to the poor prognosis conferred by pre-operative disease severity[32]. However, Child-Pugh A recipients can safely receive grafts as small as GWRW < 0.6%. It has been suggested that pre-existing portal hypertension may exacerbate the hyperperfusion seen in SFSS.
STRATEGIES TO PREVENT SFSS: MODULATING INFLOW

Since portal hyperperfusion is thought to be central to the pathogenesis of SFSS, the most popular strategies for prevention have focused on modulating inflow to the liver via inputs to the portal system. These include splenic artery modulation (igation/embolisation), portacaval shunts and less commonly, splenectomy. To date, there are no studies directly comparing outcome from these techniques.

Splenic artery modulation techniques

Splenic artery modulation (SAM) was originally performed for portal hypertension secondary to cirrhosis. It was shown to be an effective treatment for post transplant patients exhibiting signs of SFSS, probably because of the reduction in portal pressure gradient\[25\]. In patients with portal hypertension, occluding the splenic artery reduces portal flow by 52% on average\[22\]. More recently, there is increasing tendency to perform SAM as a prophylactic procedure either based on algorithms predicting high risk of SFSS pre-operatively or based on intraoperative detection of high portal flow.

Gruttadauria et al\[34\] performed splenic artery embolisation (SAE) in six patients who developed SFSS after transplantation of GWRW < 0.8% grafts. Rapid resolution of symptoms occurred post SAE. However, one patient suffered massive colligation of the spleen necessitating re-laparotomy and another suffered septic shock with consequent re-transplantation.

Two case-control series have tested the effectiveness of prophylactic splenic artery modulation\[25,28\]. Both studies found a significant reduction in portal flow following SAM and Umeda et al\[23\] were able to show a significant reduction in incidence of SFSS. Remarkably, neither group reported any cases of splenic infarction and this fortunate low complication rate was not replicated in other smaller case series\[26\]. This discrepancy in complication rates suggest splenic infarction may be reduced in experienced hands but remains a formidable problem.

Portacaval shunts

Portacaval shunting has gained favor in recent years due to its potential reversibility and to avoid possible splenic infarction\[27,28\]. Three case series where hemiportacaval shunts were constructed by anastomosing the right portal vein to the inferior vena cava have reported reasonable success in improving outcome of small for size grafts\[29,30\]. Portacaval shunts were able to reduce portal blood flow and pressure and lessen the likelihood of deranged liver function tests (LFTs) and international normalised ratio post operatively. One study\[31\] reported increased graft survival from 20% in the control group to 75% in the shunt group.

In small-for-size rat models, however, concerns have been raised over the safety of a long term shunt\[32\] where a group of rat liver transplants with large portacaval shunts showed significantly worse graft survival rates at one year compared to the small shunt or no shunt groups.

A case report from Japan where a portacaval shunt was constructed for small-for-size living donor liver transplantation (LDLT) noted progressive graft atrophy and a decision was made to close the shunt at 11 months. Fortunately this resulted in regeneration of the graft\[33\].

The natural history of a portacaval shunt is to occlude with time. In one study\[34\], 55% of shunts remained patent at six months and only 20% were patent at one year. In the shunts that remain patent, it is possible that persistent diversion of blood flow to the liver will compromise long term viability of the graft through mechanisms such as chronic ischemia. Hence shunts are likely to improve graft survival in the weeks immediately post operatively by reducing incidence of SFSS but may become a liability in the long term. Is there an optimum time, then, for electively closing the shunt?

MIDDLE HEPATIC VEIN CONTROVERSY: DONOR SAFETY VS GRAFT CONGESTION

The middle hepatic vein (MHV) is considered “dominant” in drainage of the hemiliver in 27% of cases\[34\]. A right hepaectomy without the MHV or reconstruction can induce congestion of the paramedian segments V and VIII, reducing functional capacity of the graft. Harvesting the MHV in extended hepaectomy increases the risk of complications in the donor. The questions are therefore threefold: should we harvest or reconstruct the MHV? If so, which recipients would benefit most? What is the risk to the donor?

Lee et al\[35\] reported grafts without the MHV exhibited congestion of the right median sector leading to ascites and severe LFT derangement. Kamei et al\[36\] introduced the concept of non-congestive GRWR (ncGRWR) as a better measure of graft function than size ratio alone and showed patients with ncGRWR < 0.65 developed prolonged cholestasis, one of the features of SFSS.

Other studies found no significant difference in graft survival with or without harvest of the MHV as long as a vein interpositional graft was used for anastomosis\[37,38\]. It is important to note that most studies on MHV included grafts of all sizes. If we stratify grafts by size, the importance of venous congestion emerges\[39,40\]. In a series of 120 patients where 67% had reconstruction of MHV, there was no significant benefit in venous reconstruction for a large graft. For small-for-size grafts (GWRW < 1), however, patients who did not have venous reconstruction had darged LFTs for significantly longer periods of time and also had slower regeneration of the graft (95% vs 80% at one month). In the medium term, grafts with reconstruction of the MHV had higher rates of survival at six months\[41\].

In the early days of living related and split cadaveric grafts, the decision to harvest the MHV was set by institutional policy. More recently, several centers have tried to rationalise harvesting the MHV by designing algorithms to predict recipients most likely to suffer small-for-size
syndrome. One of the earliest algorithms incorporated donor-recipient weight ratio, right lobe-to-recipient standard liver volume estimate and donor hepatic vein anatomy, including diameter and number of tributaries. This split the patients into two cohorts with comparable baseline demographics and they were able to obtain similarly low complication rates regardless of whether the MHV formed part of the graft. Later algorithms have incorporated hepatic vein dominance measured by 3D CT and congestion volumes. This is potentially better representative of the relative importance of the MHV.

Since safety of the donor is paramount in transplant surgery, it is important to quantify the risk. In one series (n = 105) where the MHV was not harvested, 13.3% of donors experienced major complications with eight patients requiring invasive paracentesis and three requiring further surgery. Does harvesting the MHV confer additional risk to the donor? Contrary to common belief, there is in fact remarkably little solid evidence to support this.

It has been noted that liver size is related to the functional demands placed upon it by the body. Hence small-for-size grafts undergo compensatory growth whereas large-for-size grafts shed cells by apoptosis. Smaller grafts have been shown to have a higher rate of regeneration despite showing signs of endothelial injury and sinusoidal congestion. However, fast regeneration is not necessarily predictive of good outcome, as a porcine small-for-size model showed that proliferative activity in nonsurviving grafts peaked earlier and higher whereas surviving grafts demonstrated a slower but maintained rise.

A body of evidence suggests liver graft regeneration is related to velocity and volume of portal flow. Park et al have demonstrated a correlation between portal venous flow or velocity to graft weight ratio with short term regeneration in LDLTs. Regenerative rates have been shown to be proportional to spleen volume and portal inflow. Cirrhotics generally experience faster regeneration compared to those undergoing transplants for other reasons, a phenomenon which is correlated to a persistent hyperdynamic portal venous circulation. However, confounding factors cannot be ruled out when comparing cirrhotics to other transplant recipients. Portal hyperflow induced shear stress and nitric oxide release have been singled out as possible mediators in stimulating liver regeneration in the setting of partial hepaectomy.

The above findings have profound implications for splenic artery ligation and portacaval shunting techniques as these may compromise compensatory regrowth.

What is the optimal portal flow that will stimulate regeneration without damaging the graft? We need studies that quantitatively correlate portal flow to both rates of regeneration and severity of graft injury. One recent study tentatively suggests a threshold of portal venous flow to graft weight of 300 mL/minutes per 100 g on post operative days one to three, based on 18 LDLTs. Above this level, LFTs were significantly more deranged. Larger, better controlled studies are needed to clarify this threshold which will have key therapeutic implications.

Portal hyperperfusion is thought to cause liver injury and defective regeneration via interleukin-6 and tumor necrosis factor (TNF)-α signalling. Tian et al report a fascinating mouse model where TNF pathways were interrupted by receptor knockout, treatment and gadolinium chloride and pentoxifylline (PTX). These mice underwent 30% liver transplantation. In the groups with TNF pathway intervention better portal flow and sinusoid perfusion was seen with reduced leukocyte adherence. Graft survival was dramatically increased: 14% in controls, 57% in TNF receptor knockout, 43% in gadolinium chloride and 86% in PTX. This elegant demonstration shows it is possible to prevent the effects of hyperperfusion injury without physically reducing flow.

**CONCLUSION**

Small-for-size syndrome has become an increasingly well recognised condition with the rise in popularity of LDLT and split cadaveric grafts. Better understanding of its pathogenesis, risk factors and strategies for prevention will improve both donor and recipient outcomes and expand the potential organ pool.

Although many significant advances have been made in understanding and managing small-for-size syndrome, much work remains to be done. Of prime importance is an internationally agreed set of diagnostic criteria for SFSS which would help us to clarify the scale of the problem and enable future studies to be standardised.

Portal hyperperfusion appears to be the most important underlying mechanism for SFSS; however, we must remember that regeneration relies on an adequate blood supply and interventions to reduce SFSS should strike a delicate balance between avoidance of hyperperfusion injury and stimulation of regeneration. Independent contribution of poor hepatic arterial flow to graft dysfunction remains to be clarified. A gold standard measurement of portal hyperperfusion, whether portal venous pressure or flow, should be agreed. Crucially, we need to establish the
threshold level of hyperperfusion that does more harm than good.

Splenic artery modulation and portacaval shunting have both shown promise in prophylaxis and treatment of SFSS in multiple case series. Evidence from randomised control trials have so far been lacking but will perhaps become feasible with more LDLT and split cadaveric grafts being performed in the future.

REFERENCES

1 European Liver Transplant Registry. Available from: URL: http://www.eltr.org
2 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: 2605-2610
3 Kiuchi T, Tanaka K, Ito T, Oike F, Ogura Y, Fujimoto Y, Ogawa K. Small-for-size graft in living donor liver transplantation: how far should we go? Liver Transplant 2003; 9: S29-S35
4 Yagi S, Iida T, Taniguchi K, Hori T, Hamada T, Fuji K, Mizuno S, Uemoto S. Impact of portal venous pressure on regeneration and graft damage after living-donor liver transplantation. Liver Transpl 2005; 11: 68-75
5 Zhuang ZG, Qian LJ, Wang BX, Zhou Y, Li QG, Xu JR, Campos BD, Johanning J, Mercer D, Grant W. Portal hyperperfusion injury as the cause of primary nonfunction in a small-for-size liver graft-successful treatment with splenic artery ligation. Liver Transplant 2005; 9: 626-628
6 Del Guercio LR, Cohn JD, Kazarain KK, Kinkhawbwalla M. A shunt equation for estimating the splenic component of portal hypertension. Am J Surg 2001; 136: 280-285
7 Fondevila C, Hessheimer AJ, Taurin P, Sanchez O, Calatayud D, de Riva N, Muñoz J, Fuster J, Rimola A, García-Valdecasas JC. Portal hyperperfusion: mechanism of injury and stimulus for regeneration in porcine small-for-size transplantation. Liver Transplant 2010; 16: 364-374
8 Kelly DM, Demetris AJ, Fung JJ, Marcos A, Zhu Y, Subbotin V, Yin L, Totsuka E, Ishii T, Lee MC, Gutierrez J, Costa G, Venkataraman R, Madaraga JR. Porcine partial liver transplantation: a novel model of the "small-for-size" liver graft. Liver Transplant 2004; 10: 253-263
9 Del Guercio LR, Cohn JD, Kazarain KK, Kinkhawbwalla M. A shunt equation for estimating the splenic component of portal hypertension. Am J Surg 2001; 136: 280-285
10 Kelly DM, Demetris AJ, Fung JJ, Marcos A, Zhu Y, Subbotin V, Yin L, Totsuka E, Ishii T, Lee MC, Gutierrez J, Costa G, Venkataraman R, Madaraga JR. Porcine partial liver transplantation: a novel model of the "small-for-size" liver graft. Liver Transplant 2004; 10: 253-263
11 Del Guercio LR, Cohn JD, Kazarain KK, Kinkhawbwalla M. A shunt equation for estimating the splenic component of portal hypertension. Am J Surg 2001; 136: 280-285
12 Lautt WW. Regulatory processes interacting to maintain hepatic blood flow constancy: Vascular compliance, hepatic arterial buffer response, hepatoportal reflex, liver regeneration, escape from vasocostriction. Hepatol Res 2007; 37: 891-903
13 Lautt WW, Legane DJ, Ezzat WR. Quantitation of the hepatic arterial buffer response to graded changes in portal blood flow. Gastroenterology 1990; 98: 1024-1028
14 Smyrniotis V, Kostopanagiotou G, Kondi A, Gamaletesos E, Theodoraki K, Kehagias D, Mystakidou K, Kontis J. Hemo-dynamic interaction between portal vein and hepatic artery flow in small-for-size split liver transplantation. Transplant Int 2002; 15: 355-360
15 Kelly DM, Zhu X, Shiba H, Irefin S, Treniti L, Cocieri A, Diago T, Wang LF, Quintini C, Chen Z, Alster J, Nakagawa S, Miller C, Demetris A, Fung JJ. Adenosine restores the hepatic artery buffer response and improves survival in a porcine model of small-for-size syndrome. Liver Transplant 2009; 15: 1448-1457
16 Kiuchi T, Tanaka K. Living-related donor liver transplantation: status quo in Kyoto, Japan. Transplant Proc 1998; 30: 687-691
17 Sugawara Y, Makuuchi M, Takayama T, Imamura H, Dowa-ki S, Mizuta K, Kawarasaki H, Hashizume K. Small-for-size grafts in living-related liver transplantation. J Am Coll Surg 2001; 192: 510-513
18 Hill MJ, Hughes M, ie T, Cohen M, Lake J, Payne WD, Humar A. Graft weight/recipient weight ratio: how well does it predict outcome after partial liver transplants? Liver Transplant 2009; 15: 1056-1062
19 Shimada M, Iijichi H, Yonemura Y, Harada N, Shiotani S, Ninomiya M, Yoshizumi T, Soejima Y, Suehiro T, Maehara Y. Is graft size a major risk factor in living-donor adult liver transplantation? Transplant Int 2004; 17: 310-316
20 Ben-Haim M, Emre S, Fishbein TM, Sheiner PA, Bodian CA, Kim-Schluger L, Schwartz ME, Miller CM. Critical graft size in adult-to-adult living-donor liver transplantation: impact of the recipient’s disease. Liver Transplant 2001; 7: 948-953
21 Lo CM, Liu CL, Fan ST. Portal hyperperfusion injury as the cause of primary nonfunction in a small-for-size liver graft. Liver Transplant 2005; 9: 559-567
22 Del Guercio LR, Cohn JD, Kazarain KK, Kinkhawbwalla M. A shunt equation for estimating the splenic component of portal hypertension. Am J Surg 1978; 135: 70-75
23 Gruttadauria S, Mandala L, Miraglia R, Caruso S, Minervini M, Biondo D, Volpes R, Vizzini G, Marsh JW, Luca A, Marcos A, Gridelli B. Successful treatment of small-for-size syndrome in adult-to-adult living-related liver transplantation: single center series. Clin Transplant 2007; 21: 761-766
24 Troisi R, Cammu G, Militerno G, De Baerdemaeker L, Decruyenaere J, Hoste E, Snoepts P, Colle I, Van Vlierberghe H, Petrovic M, Voet D, Mortier E, Hesse UJ, de Hemptinne B. Modulation of portal graft inflow: a necessity in adult living-donor liver transplantation? Ann Surg 2003; 237: 429-436
25 Umaeda Y, Yagi T, Tadamori H, Matsukawa H, Matsuoka S, Shinoura S, Mizuno K, Yoshida R, Iwamoto T, Satoh D, Tanaka N. Effects of prophylactic splenic artery modulation on portal perfusion and liver regeneration in small-for-size graft. Transplantation 2008; 86: 673-677
26 Singhal A, Goyal N, Gupta VV. Delayed splenic artery occlusion for treatment of established small-for-size syndrome after partial liver transplantation. Liver Transpl 2009; 15: 1381-1382
27 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 2008; 14: 671-675
28 Ikegami T, Imura S, Arakawa Y, Shimada M. Transient portocaval shunt for a small-for-size graft in living donor liver transplantation. Liver Transplant 2008; 14: 262; author reply 263
29 Botha JF, Langnas AN, Campos BD, Grant WJ, Freise CE, Ascher NL, Mercer DF, Roberts JP. Left lobe adult-to-adult living donor liver transplantation. Liver Transplant 2010; 16: 649-657
30 Troisi R, Ricciardi S, Sneets P, Petrovic M, Van Maele G, Collis I, Van Vlierberghe H, de Hemptinne B. Effects of hemiportocaval shunts for inflow modulation on the outcome of small-for-size grafts in living donor liver transplantation. Am J Transplant 2005; 5: 1397-1404
31 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 transpla-
placation. Am J Transplant. 2008; 8: 847-853
32 Nakano T, Lai CY, Goto S, Hsu LW, Huang TL, Chen TY, Tsang LC, Chen CL, Cheng YF. Significance of portosystemic shunt on graft survival in liver transplantation: a rat model. Transplant Proc. 2008; 40: 2515-2516
33 Oura T, Taniguchi M, Shimamura T, Suzuki T, Yamashita K, Uno M, Goto R, Watanabe M, Kiyama T, Matsushita M, Furukawa H, Todo S. 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: 250-252
34 Radtke A, Sotiropoulos GC, Spourakis G, Molmenti EP, Schroeder T, Saner FH, Beckebaum S, Broelsch CE, Broering DC, Malago M. Hepatic venous drainage: how much can we learn from imaging studies? Anatomo-functional classification derived from three-dimensional computed tomography reconstructions. Transplantation. 2010; 89: 1518-1525
35 Lee S, Park K, Hwang S, Lee Y, Choi D, Kim K, Koh K, Han S, Choi K, Hwang K, Makuch M, Sugawara Y, Min P. Congestion of right liver graft in living donor liver transplantation. Transplantation. 2001; 71: 812-814
36 Kamei H, Fujimoto Y, Nagai S, Suda R, Yamamoto H, Kishi T. Impact of non-congestive graft size in living donor liver transplantation: new indicator for additional vein reconstruction in right liver graft. Liver Transpl. 2007; 13: 1295-1301
37 Kasahara M, Takada Y, Fujimoto Y, Ogura Y, Ogawa K, Uryuhara K, Yonekawa Y, Ueda M, Egawa H, Tanaka K. Impact of right lobe with middle hepatic vein graft in living-donor liver transplantation. Am J Transplant. 2005; 5: 1339-1346
38 Adham M, Dumortier J, Abdelaal A, Sagnard P, Boucaud C, Boilott O. Does middle hepatic vein omission in a right split graft affect the outcome of liver transplantation? A comparative study of right split livers with and without the middle hepatic vein. Liver Transpl. 2007; 13: 829-837
39 Detry O, De Roover A, Coimbra C, Delwaide J, Hans MF, Monard J, Kaba A, Joris J, Honore P, Meurisse M. Right liver living related liver transplantation in adults without venous drainage of the paramedian sector. Transplant Proc. 2005; 37: 2865-2868
40 De Carlis L, Lautiero A, Giaconami A, Slim AO, Pirotta V, Mangoni J, Mihaylov P. Adult living donor liver transplantation with right lobe graft: the venous outflow management in the Milan-Niguarda experience. Transplant Proc. 2008; 40: 1944-1946
41 Tashiro H, Ohdan H, Itamoto T, Fudaya H, Amano H, Osbata A, Ishitora K, Iriyama T, Obara M, Tabara H, Banshoudani M, Tanimoto Y, Ishufuro M, Asahara T. Using recipient's middle hepatic vein for drainage of the right paramedian sector in right liver graft. Transplantation. 2008; 86: 1565-1571
42 de Villa VH, Chen CL, Chen YS, Wang CC, Lin CC, Cheng YF, Huang TL, Jawan B, Eng HL. Right lobe living donor transplantation-addressing the middle hepatic vein controversy. Ann Surg 2003; 238: 275-282
43 Radtke A, Spourakis G, Sotiropoulos GC, Beckebaum S, Molmenti EP, Saner FH, Schroeder T, Nadalin S, Schenk A, Lang H, Malago M, Broelsch CE. Donorrecipient algorithm for management of the middle hepatic vein in right graft live donor liver transplantation. Am J Surg. 2010; 199: 708-715
44 Dayangac M, Taner CB, Balci D, Memi I, Yaprak O, Akin B, Duran C, Killi R, Ayanoglu O, Yuzer Y, Tokay Y. Use of middle hepatic vein in right living donor liver transplantation. Transpl Int 2010; 23: 285-291
45 Fukuhara T, Umeda K, Toshima T, Takeishi K, Morita K, Nagata S, Sugimachi K, Ikegami T, Gion T, Soejima Y, Takeshita A, Maehara Y. Congestion of the donor remnant right liver after extended left lobe donation. TransplantProc. 2009; 22: 837-844
46 Scatton O, Plass M, Dondero F, Vilgrain V, Sauvanet A, Belghiti J. Impact of localized congestion related to venous deprivation after hepatectomy. Surgery 2008; 143: 483-489
47 Fausto N. Liver regeneration: from laboratory to clinic. Liver Transpl 2001; 7: 835-844
48 Nishizaka T, Ikegami T, Hiroshige S, Hashimoto K, Uchiyama H, Yoshizumi T, Kishikawa K, Shimada M, Sugimachi K. Small graft for living donor liver transplantation. Ann Surg. 2001; 233: 575-580
49 Lee SG, Hwang S, Lee YJ, Park KM, Jeon HB, Min PC. Regeneration of graft liver in adult-to-adult living donor liver transplantation using a left lobe graft. J Korean Med Sci 1998; 13: 350-354
50 Park MY, Lee YJ, Rha SE, Oh SN, Byun JY, Kim DC. Correlation of portal venous velocity and portal venous flow with short-term graft regeneration in recipients of living donor liver transplants. Transplant Proc. 2008; 40: 1488-1491
51 Chen HL, Chen CL, Huang TL, Chen TY, Tsang LL, Ou HY, Yu CY, Cheng YF. Regeneration rate of left liver grafts in adult living donor liver transplant. Transplant Proc. 2010; 42: 699-700
52 Eguchi S, Yanaka K, Sugiyama N, Okudaira S, Furui J, Kane-matsu T. Relationship between portal venous flow and liver regeneration in patients after living donor right-lobe liver transplantation. Liver Transpl 2003; 9: 547-551
53 Schoen JM, Wang HH, Minuk GY, Lautt WW. Shear stress-induced nitric oxide release triggers the liver regeneration cascade. Nitric Oxide 2001; 5: 453-464
54 Sato Y, Koyama S, Tsukada K, Hatakeyama K. Acute portal hypertension reflecting shear stress as a trigger of liver regeneration following partial hepatectomy. Surg Today 1997; 27: 518-526
55 Jiang SM, Zhou GW, Zhang R, Peng CH, Yan JQ, Wan L, Shen C, Chen H, Li QY, Shen BY, Li HW. Role of splanchnic hemodynamics in liver regeneration after living donor liver transplantation. Liver Transpl 2009; 15: 1043-1049
56 Tian Y, Jochum W, Georgiev P, Moritz W, Graf R, Clavien PA. Kupffer cell-dependent TNF-alpha signaling mediates injury in the arterialized small-for-size liver transplantation in the mouse. Proc Natl Acad Sci USA 2006; 103: 4596-4603

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