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Perspective:

Dual liver transplantation*

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Reperfusion is the key strategy in acute ST-segment elevation myocardial infarction (STEMI) care, and it is time-dependent. Shortening the time from symptom to reperfusion and choosing the optimal reperfusion strategy for STEMI patients are great challenges in practice. We need to improve upon the problems of low reperfusion rate, non-standardized treatment, and economic burden in STEMI care. This article briefly reviews the current status of reperfusion strategy in STEMI care, and also introduces what we will do to bridge the gap between the guidelines and implementation in the clinical setting through the upcoming China STEMI early reperfusion program.

1 Introduction

Liver transplantation is an efficacious therapy for end-stage liver diseases of various etiologies, but a huge gap remains between the number of patients who are waiting for the liver transplant and the number of organs available. In order to obtain donor organs to the greatest extent for adult and pediatric recipients, novel surgical techniques have evolved, including split liver transplantation (SLT) from cadaveric donor and living donor liver transplantation (LDLT) (Malagó *et al*., 1997).

In SLT, two grafts are harvested by segmenting one liver from a cadaveric donor. The prognosis of SLT has been inferior to that of whole organ transplants on account of a high incidence of primary nonfunctioning (PNF) and technical problems (Houssin *et al*., 1993). Reformative SLT, where the liver is divided into two parts in situ when the donor's heart is still beating, has better survival rates, primarily as the result of reduced ischemic injury. SLT is limited by the fact that the number of children candidates is lower than that of adult candidates for liver transplantation. The concept of using a split liver technique to obtain grafts for two adults has been extremely restricted for the last ten years, largely since the size of the left lobe is insufficient for most adult recipients (Yamaoka *et al*., 1994; Colledan *et al*., 1999).

The unceasing shortage of organs has led to development of other innovative techniques to maximize the donor organ access, namely LDLT, which has evolved from the procedures for SLT. The introduction of LDLT has been one of the most remarkable milestones in the field of liver transplantation. Since 1989, more than 12 000 LDLTs have been performed worldwide (Lo *et al*., 1999; Middleton *et al*., 2006; Sugawara and Makuuchi, 2006). LDLT has several theoretical advantages: (1) Transplantation can be performed on an elective basis before irretrievable decompensation of the recipient; (2) The

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graft is usually of excellent quality (Nadalin *et al*., 2004); (3) Ischemic time is relatively short; (4) LDLT raises the feasibility of liver graft for recipients who might otherwise not be qualified for standard deceased donor liver transplantation (Malagó *et al*., 2006). However, the extreme hazard of this pattern increases the morbidity and mortality potential for donor and recipient to 200%.

With the objective of achieving maximal donor safety by minimizing the mass of resected liver, the technique of "dual liver" adult-to-adult LDLT has been introduced, in which two lobe grafts are removed from two donors and grafted into one recipient (Lee *et al*., 2001a; Lee *et al*., 2001b; Kaihara *et al*., 2002; Wang *et al*., 2006; Broering *et al*., 2007). Lee *et al*. (2001a) first proposed the concept of dual left lobe grafts for liver transplantation and performed the first in 2001. As of June 2008, more than two hundred dual graft liver transplantations have been successfully performed at the Asan Medical Center in Korea (Zhang *et al*., 2008). To date, cases of dual liver transplantation have been reported worldwide (Table 1). Little is known about the indications and contraindications of dual liver transplantation, and there are no selection standards for dual grafts. There are no animal model reports of dual liver transplantation. Here we review 25 cases of dual liver transplantation, for which the medical data are available (Table 2).

2 Why was the dual liver transplantation adopted, simultaneously taking the risks of double donors even when SLT and LDLT are available?

A healthy individual, usually a relative or friend to the recipient, voluntarily donates part of liver. Furthermore, a surgeon can feel great pressure in order to ensure that operations are successful for both donors and recipients. Balancing the safety of the donor with a satisfying outcome of the recipient is a crucial issue in the process of living donation. The ethical issue of putting two donors at risk simultaneously for one recipient is contentious.

Previous studies indicate that at least 50% of the standard liver volume of the recipient is required to provide adequate functional hepatocytes to maintain the basic life (Fan *et al*., 2000). The metabolic demands of a larger recipient will not be met by a left lobe from a relatively small donor. The potential solutions to this problem are to raise the extent of resection of donor liver by the way of harvesting the right lobe of the liver, which theoretically accounts for 60% to 70% of the total liver mass, or to transplant dual grafts into one recipient. Harvesting the right lobe of the donor is not always safe, depending primarily on the volume of the remaining left lobe (Kawasaki *et al*., 1998). Even though the recipient may receive an adequate graft volume, the remaining left lobe may be not enough for donor safety. In this case, a possible and safe solution is dual left lobe or left lateral segment from two living donors which can address the problem of graft-size insufficiency and maximize donor safety. Furthermore, if the recipient requires a larger graft liver volume than the total volume of the two potential living donors' left lobes, and if right lobe harvest from one of two potential donors is deemed to be safe, one right lobe and one left lobe are the best match for a single recipient to avoid a small-for-size graft problem.

In adult-to-adult LDLT, since a small left lobe graft cannot meet the metabolic demand of recipients in most cases, dual grafts from two living donors can help to alleviate the problem of small-for-size graft syndrome (SFSGS) and yet secure the safety of the

Table 1 Published cases of dual liver transplantation

Reference	Journal	Number of cases	Nation
Lee *et al*., 2001a	*Surgery*	1	Korea
Lee *et al*., 2001b	*Transplantation Proceedings*	17	Korea
Kaihara *et al*., 2002	*Surgery*	1	Japan
Hwang *et al*., 2006	*Liver Transplantation*	163	Korea
Broering *et al*., 2007	*Liver Transplantation*	2	Germany
Soejima *et al*., 2008	*American Journal of Transplantation*	1	Japan
Zhang *et al*., 2008	*Hepatogastroenterology*	1	China
Yang *et al*., 2009	*Surgery*	3	Taiwan (China)

Table 2 Cases of dual liver transplantation in the world

No.	Recipient					Donor								
						Left side graft				Right side graft				
	Disease	Sex/ age (year)	Weight[a] (kg)	SLV[b] (cm^3)	Blood	Relation	Sex/ age (year)	Weight (g)/ volume (cm^3)	Lobe type/ Blood	Relation	Sex/ age (year)	Weight (g)/ volume (cm^3)	Lobe type/ blood	Result
1	HBV-LC, HCC	M/28	59 (1.5%)	1057 (53%)	A	Sister	F/34	310/300	LL/A	Sister	F/31	310/260	LL/A	Good
2	HBV-LC	M/35	70 (1.2%)	1276 (65.4%)	B	Cadaveric	F	230/270	LL/O	Mother		630/560 (10% fat)	RL/O	Good
3	HCV-LC, HCC	M/51	95 (0.86%)	1824 (54.6%)		Wife	F	350/394	LL	Son	M	470/591	RL	Good
4	HBV-HCC	F/58	64.9 (1.46%)	1311 (81.1%)		Son	M/30	600/793 (70% fat)	LLS	Samaritan	M/>45	350/370 (10% fat)	LLS	Good
5	HBV-LC	M/52	83.7 (0.79%)	1498 (52.4%)		Daughter	F/23	370/363	LL	Brother	M/37	290/422 (80% fat)	LLS	Good
6	HCV-LC	M/57	65 (0.82%)	1463 (45.7%)		Son	M/24	346/433	LL	Brother-in-law	M/33	186/235	LLS	Good
7	HBV-LC	M/67	97 (0.80%)	1884 (54.5%)		Nephew	M/40	173/386	LLS	Son	M/20	538/640	RL	Good
8	HBV-LC	M/48		1314	A	Brother	M/38	400 (10% fat)	LL/A	Daughter	F/20	270	LL/A	Good
9	HBV-LC	M/41		1132	B	Uncle	M/49	320 (30% fat)	LL/B	Cadaver	F/27	360 (LLS)	LLS/O	Atrophy of RSG
10	HBV-FHF	M/28		1356	A	Brother	M/27	400 (20% fat)	LL/A	Brother	M/34	300 (10% fat)	LL/A	Good
12	HBV-LC	M/35		1266	A	Brother-in-law	M/29	350 (40% fat)	LL/A	Wife	F/38	300 (15% fat)	LL/A	Atrophy of RSG
13	HBV-LC, H-R	F/55		1400	B	Daughter	F/26	300	LL/B	Son-in-law	M/32	500	LL/B	Dead
14	HBV-LC	M/41		1160	A	Brother	M/47	460	LL/A	Friend	M/38	350 (50% fat)	LL/A	Good
15	HBV-FHF	M/33		1316	O	Brother-in-law	M/28	550 (40% fat)	LL/O	Father	M/60	380 (LLS)	LLS/O	Good
16	HBV-LC, HCC	M/44		1393	O	Friend	M/44	400 (5% fat)	LL/O	Cousin	M/35	370 (5% fat)	LL/O	Good
17	HBV-LC	M/44		1294	A	Wife	F/42	290 (5% fat)	LL/O	Nephew	M/27	365	LL/O	Dead
18	HBV-LC, H-R	M/42		1174	O	Wife	F/40	400 (10% fat)	LL/O	Son	M/22	300 (5% fat)	LL/O	Good
19	HBV-LC, H-R	M/46		1174	B	Brother	M/36	320	LL/B	Brother-in-law	M/40	350 (30% fat) (LLS)	LLS/B	Good
20	HBV-LC	M/49		1245	A	Son	M/21	350	LL/A	Nephew	F/25	230 (LLS)	LLS/O	Atrophy of RSG
21	HBV-LC	M/47		1449	O	Son	M/19	400 (10% fat)	LL/O	Brother	M/34	340 (5% fat)	LL/O	Dead
22	HBV-LC	M/42		1442	O	Cousin	M/29	360 (55% fat)	LL/O	Wife	F/38	570 (3% fat) (RL)	RL/O	Good
23	HCV-LC, HBV-LC, HCC	M/55		1294	O	Brother	M/35	450 (10% fat)	LL/O	Son	M/23	340	LL/O	Good
24	HCV-LC	F/62		1061	B	Son	M/33	350	LL/B	Daughter	F/31	300 (10% fat)	LL/B	Good
25	HBV-LC	M/42		1294	B	Nephew	M/18	450	LL/B	Pastot	M/40	350 (25% fat)	LL/B	Good

SLV, standard liver volume of the recipient; HBV-LC, hepatitis B virus liver cirrhosis; FHF, fulminant hepatic failure; H-R syndrome, hepato-renal syndrome; HCC, hepatocellular carcinoma; HCV-LC, hepatitis C virus liver cirrhosis; LL, left lobe; LLS, left lateral segment; RL, right lobe; LSG, left side graft; RSG, right side graft. [a] The data in the parenthese are the ratios of grafts to recipients' weight; [b] The data in the parenthese are the ratios of graft volume/standard liver volume

donor in that situation, especially in countries with extreme scarcity of deceased donors. However, the threat to each donor in dual graft LDLT may not be different from that to a donor in single donor LDLT. Therefore, a combined risk of two donors may be double of that of a single donor. In LDLT, donor safety has first priority. Therefore, a substantial proportion of patients with end-stage liver disease waiting for LDLT have no choice but to give up the opportunity for cure due to concern about donor safety, mainly associated with the small remaining liver volume in the donor. Although there will be constant ethical concerns about placing two donors at risk for one patient, we believe that dual graft LDLT can offer an effective and safe therapeutic option for a family who hopes to save one of their own family members.

3 What guidelines must be observed when performing dual liver transplantation?

The mortality of donor is about 0.15%–0.20% where the number of donor deaths reported has reached 14 (Trotter *et al*., 2006). While the donor mortality is estimated to be approximately 0.1% after left lateral segmentectomy (Otte, 2003), the risk of death for donors of a right lobe ranges from 0.4% to 0.5% (Moon *et al*., 2006). Until 2006, 3 donors have died after donation of the left lateral lobe, and 12 deaths of right lobe donors have been reported worldwide (Florman and Miller, 2006).

How to optimize graft volume is still a controversial issue. At present, there are two standards worldwide: one is ratio of grafts to recipients' weight (GRWR) and the other is ratio of grafts volume to recipients' standard liver volume (GV/SLV). It is generally thought that the former should be more than 0.8% (Fan *et al*., 2000), and the latter should be more than 40% (Kawasaki *et al*., 1998). According to the Fan *et al*. (2000) criteria, the volume of remnant liver should exceed 30%, while Lee *et al*. (2001b) believes that the volume of remnant liver should exceed 35% (Kawasaki *et al*., 1998). Previous study has shown, in Table 2 in the first seven cases, average GRWR and GV/SLV to be 1.06% and 58.1%, respectively, with good results, but from Cases 8 to 25, GV/SLV ranges from 46.6% to 78.9% with three patients dying (Lee *et al*., 2001b).

Dual left lobe or lateral segment transplantation may be considered in certain situations. Firstly, is the donor's left liver lobe too small to meet the metabolic demand of the recipient (Lee *et al*., 2001b)? Secondly, is the proportion of the donor's right lobe to the left lobe unusually high (greater than 70% of total liver volume) (Lee *et al*., 2001b), so that right lobectomy in the donor would lead to a high risk of liver insufficiency in the immediate postoperative period? Thirdly, the total volume of the dual graft should be at least 50% of the standard liver volume of the recipient, and the remaining liver in the donor should be more than 35% of the standard liver volume of the donor. If the donor is of marginal liver size, the size of donor should be increased. There is no available criterion for marginal liver donor presently. Of 25 cases, 7 cases are dual grafts with different steatosis from 3% to 70% fat, and 10 cases are dual grafts with different steatosis from 10% to 81% fat. The maximal GV/SLV was 81.1%. Moon *et al*. (2006) extended the indications for dual liver transplantation to using marginal grafts such as fatty liver grafts. They transplanted dual left lobe grafts into a single recipient, and rapid improvement in the graft steatosis was found within two weeks after transplantation, confirmed by computed tomography (CT) scan and biopsies (Moon *et al*., 2006). Increased volume of the marginal donor is necessary in dual liver transplantation.

4 What are the differences in surgical technique between dual liver transplantation and SLT and LDLT?

The initial series of dual liver transplantations was reported by Lee *et al*. (2001b). According to their report, 94% (16/17) of patients received a dual left lobe or one left and one lateral segment graft, and only 6% (1/17) received one left and one right lobe graft. To justify placing two donors at safety, they tried to use two lateral segment or left lobe grafts, as long as the sum of left lateral segment grafts exceeded 50% of the SLV of the recipient.

To date, four kinds of dual liver transplantation techniques have been described. Of 25 patients, 14 received two left lobes, 6 received one left lobe and one left lateral segment, and 4 received one right lobe

and one left lobe, 1 received dual left lateral lobe (Table 2).

For the graft of two left lobes or one left lobe and left lateral lobe, the differences are as follows (Lee *et al*., 2001b). (1) The second liver graft need to be rotated 180° and heterotopically positioned to the right upper quadrant after the first liver graft is orthotopically implanted at the original left position. (2) The bile duct is reconstructed by duct-to-duct anastomosis before portal vein and hepatic vein anastomoses. The alterations to surgical technique arise mostly during implantation of the heterotopic second left lobe graft. The rotation of the heterotopic second liver graft through 180° in sagittal orientation brings the hilar structures into a reversed position. Therefore, the bile duct comes to lie behind the portal vein and the hepatic artery. This makes the hepaticojejunostomy of the second liver graft difficult with poor access once the portal vein anastomosis is made. (3) An interposition vein graft obtained from cadaveric iliac vein or vena cava, or from the recipient's umbilical vein is frequently necessary to bridge the gap between the recipient's right hepatic vein and the hepatic venous end of the liver graft. (4) A tissue expander filled with saline solution can be placed underneath the graft to support it when the heterotopically positioned left lobe or lateral segment graft is small with resulting undue tension on the hilar anastomosis.

Regarding the grafts of right lobe and left lobe, the match of the grafts and recipient in spatial position makes the operation relatively easy. There is no need to heterotopically rotate the graft through 180°. With regard to technical aspects, a right and a left lobe combination is probably an ideal option in dual graft LDLT. The positioning of each graft is anatomically natural and does not require any supportive device.

5 Clinically underlying danger

The left lobe and left lateral lobe implanted in the right side after heterotopic rotation display particular haemodynamic properties. There can be some competition in blood supply between the two grafts. Lee *et al*. (2001b) reported two right-sided heterotopic grafts undergoing atrophy, which was considered to be the result of portal venous blood flow favoring the left-sided orthotopic graft.

The immune microenvironment may be more complicated when two grafts become the target of rejection. There is a risk of rejection not only between two grafts and recipient but also between grafts. Lee *et al*. (2001b) reported that acute rejection was found by biopsy in both orthotopic and heterotopic grafts simultaneously.

In the 25 cases reported, three patients died. Causes of death included left-sided liver graft necrosis and post-transplant intestinal gangrene, cerebral hemorrhage, and brain-stem herniation with good liver function. Survival time is difficult to report because of incomplete data.

Aside from donor safety and graft-to-recipient size match, ABO-compatibility has been regarded as an essential prerequisite for successful LDLT. However, the outcome of ABO-incompatible LDLT has improved since the adoption of a novel strategy for overcoming the ABO blood group barrier (Egawa *et al*., 2007; Kawagishi and Satomi, 2008). One study has shown that an ABO-incompatible graft can be used as one component of dual graft LDLT if the other graft is ABO compatible. The recipient was administered a single dose of rituximab two weeks before LT. Plasma exchange (PE) with blood-type AB fresh frozen plasma was performed, with the frequency and timing of PE dependent on hemaglutinin (HA) titer, with the goal being an antibody titer 1:8 or less before LT. The result showed that dual graft LDLT with a combination of ABOi and ABOc grafts can be a feasible option to simultaneously overcome both SFSG syndrome and the ABO blood group barrier (Song *et al*., 2010).

6 What should we do for clinical practice?

In the research field, the animal model of whole-size and reduced-size liver transplantation in both rat and mouse has been successfully established and is widely used. There is an essential need to establish an animal model of dual liver transplantation to lay a basic foundation for clinical practice. Regarding the difficulties in microsurgery for the whole-size and reduced-size liver transplantation in both rat and mouse, we can imagine that a great challenge needs to be faced for the establishment of an animal model of dual liver transplantation in rat

and mouse. In our research group, we took great efforts to successfully establish a rat model of dual liver transplantation which will help scientists and clinicians to explore the unknown field of dual liver transplantation (Zhang *et al*., 2012).

In short, although LDLT using dual lobe grafts takes more effort and is a technically more complicated procedure, it is safely feasible and can increase the donor pool and contribute to the practice of adult-to-adult LDLT. However, further study is needed to evaluate the efficacy of this modality. Whenever deciding to perform LDLT, the possibility of dual graft LDLT should be evaluated and discussed to minimize donor risk.

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