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GUIDELINES FOR CLINICAL PRACTICE

Donation after cardio-circulatory death liver transplantation

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Abstract

The renewed interest in donation after cardio-circulatory death (DCD) started in the 1990s following the limited success of the transplant community to expand the donation after brain-death (DBD) organ supply and following the request of potential DCD families. Since then, DCD organ procurement and transplantation activities have rapidly expanded, particularly for non-vital organs, like kidneys. In liver transplantation (LT), DCD donors are a valuable organ source that helps to decrease the mortality rate on the waiting lists and to increase the availability of organs for transplantation despite a higher risk of early graft dysfunction, more frequent vascular and ischemia-type biliary lesions, higher rates of re-listing and re-transplantation and lower graft survival, which are obviously due to the inevitable warm ischemia occurring during the declaration of death and organ retrieval process. Experimental strategies intervening in both donors and recipients at different phases of the transplantation process have focused on the attenuation of ischemia-reperfusion injury and already gained encouraging results, and some of them have found their way from pre-clinical success into clinical reality. The future of DCD-LT is promising. Concerted efforts should concentrate on the identification of suitable donors (probably Maastricht category Ⅲ DCD donors), better donor and recipient matching (high risk donors to low risk recipients), use of advanced organ preservation techniques (oxygenated hypothermic machine perfusion, normothermic machine perfusion, venous systemic oxygen persufflation), and pharmacological modulation (probably a multi-factorial biologic modulation strategy) so that DCD liver allografts could be safely utilized and attain equivalent results as DBD-LT.

Key words: Non-heart-beating donation; Complication; Bile duct; Allocation; Ischemia; Ischemia-reperfusion injury; Liver disease

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INTRODUCTION

The first human liver transplantations (LT) were performed from donation after cardio-circulatory death (DCD) in the 1960s[1-4]. DCD-LT was nonetheless almost universally abandoned in the following two decades, given the well-recognized Harvard brain-dead concept in 1968 and given the better results of LT originating from donation after brain death (DBD)[5]. In 1983, LT was approved as a therapeutic modality for end-stage liver diseases after a long period considered as an experimental procedure. The renewed interest in DCD donors started in the 1990s following the limited success of the transplant community to expand the DBD organ supply and following the request of potential DCD families.

If DCD kidneys are increasingly accepted around the world[6], the use of DCD livers remains limited in experienced transplant centers due to higher risks of primary graft dysfunction and biliary complications as well as a lack of a reliable viability testing prior to liver implantation. However the number of DCD-LT increased rapidly over the past decade. In the United States, 276 DCD liver transplants were performed in 2008 compared to only 23 cases in 1999, making up 5% of the deceased donor (DD) liver transplants[7-10]. The same trend was observed in the United Kingdom[11-13], Spain[14], Netherlands[15] and Belgium[15,16]. Netherlands had the highest rate of DCD- over DD-LT in the world (22.5% in 2008)[15]. France has just initiated its DCD-LT program since 2010[17]. In Japan, although DCD donors were the essential DD source, its use was reserved mainly for kidney, pancreas and islet transplantation[18]. Using a mathematical model to analyze the potential impact of a DCD policy on LT programs, Chaib reported if 1%, 5% and 10% of deceased individuals became DCD donors, there would be 8%, 27% and 37% relative reductions in the size of waiting list, respectively[19]. The use of DCD livers could increase the supply of transplants by 53%[20]. Centers with active DCD-LT programs usually reported 4%-10% rates of LT from the DCD source[21]. The potential impact of DCD use on the DBD availability is also a controversial issue. Controlled DCD programs might negatively influenced DBD activity in Belgium, Netherlands and United Kingdom while uncontrolled DCD donors seemed to be a clear additional source of organs for transplantation in France and Spain[22].

Most countries use Maastricht-category-3 DCD donors for LT, except France and Spain, where categories 1 and 2 are exclusively used due to legal interdiction of discontinuation of therapy in irreversibly brain-injured individuals[17,23,24]. German law prohibits any DCD organ procurement and transplant activity. In Italy, death of a human being must be declared 20 min after cardiac arrest using continuous electrocardiography. The procedure therefore will enable, at best, retrieval of only a few marginal kidneys and some tissues, and will not be helpful for patients on LT waiting lists[25]. This article is aimed at reviewing mono- and multi-centric DCD-LT outcomes, experimental strategies on animal models to optimize the utilization of this donor source and its future development.

DIFFERENCES BETWEEN DCD AND DBD DONORS PERTINENT TO LT OUTCOMES

Generally results of DCD-LT are inferior to those from DBD-LT with regard to both short-and long-term graft and patient survival as well as post-transplant morbidity. Expected DCD-LT outcomes could be explained by inherent differences between DCD and DBD donors in circumstances of death, warm ischemia time (WIT) and donor cause of death. Consequently, a different strategy of DCD use in terms of logistics of organ retrieval and preservation, allocation and recipient selection appears necessary to guarantee acceptable results. These differences will be briefly discussed prior to considering results of DCD-LT in detail.

Circumstances of death and consequent warm ischemia time

In DCD, donor death is diagnosed on the basis of irreversible cessation of cardio-pulmonary function instead of conventional neurologic criteria. As a result, organs from DCD donors are subjected to a period of hypotension, hypoxia and acirculation prior to organ procurement and this WIT adversely affects tissue viability and graft function after transplantation[26]. An international classification of DCD donors into 4 categories was first proposed in 1995 and widely accepted up to now[27]. New DCD categories have been recently suggested in Spain[28,29], Italy[30] and Belgium[31]. The length of WIT varies greatly according to the type of DCD process. It is longest among uncontrolled category -1 and -2 (usually 90-120 min) and shorter among controlled category -3 and -4 DCD donors (usually 20-30 min). In brain death, issues related to donor warm ischemia are eliminated because DBD donors have an effective natural organ perfusion and a potentially well-preserved organ function and WIT is thus nearly equal to zero.

However, WIT is heterogeneously defined among authors[32]. In the controlled DCD context, the commonest definition is the time interval between withdrawal of both ventilator and cardiac support to start of cold flushing of the organ[33,34]. This definition includes the no-touch period and the time of death declaration and is proposed to have two phases (withdrawal and acirculatory phases). Other authors used a blood pressure (BP) or oxygen saturation threshold below which would be defined as the beginning of true WIT (systolic or mean BP < 35-60 mmHg, oxygen saturation < 25%-70% or unreadable)[35-42]. de Vera *et al*[34] did not use a BP threshold to define the start of WIT because tissues are still hypoxic in a DCD donor who maintains a BP but has ceased to ventilate. It is unknown at what BP or oxygen saturation the liver parenchyma and biliary system undergo irrecoverable injury[43]. The first international Non-Heart Beating Donor workshop in Maastricht in 1995

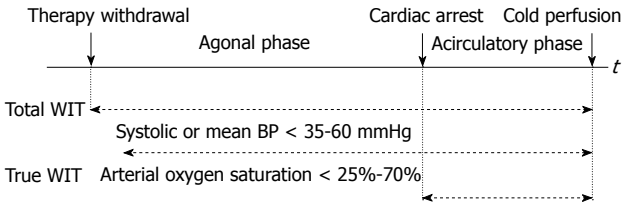

Figure 1 Different ways of warm ischemia time definition in the controlled donation after cardio-circulatory death setting (see text for more details). True warm ischemia time (WIT) is also called complete or functional WIT; Total WIT is also called overall WIT; Agonal phase is also called withdrawal phase. BP: Blood pressure; *t*: Time.

suggested WIT should be calculated from the moment of cardiac arrest until the start of hypothermic flush-out[44]. This definition may be useful for consistency but is inaccurate at the cellular level. Hypoxia starts when the blood flow or oxygenation no longer meets cellular metabolic needs[37]. The start of WIT may be chosen prior to asystole, and the end of WIT may be at or after aortic flushing[45]. Apparently a well-accepted definition of donor organ ischemic times is needed to standardize nomenclature and allow accurate comparisons of individual DCD studies[46,47] (Figure 1).

In transplant practice, WIT should be minimized as much as possible. For controlled DCD donors, the possibility to predict whether a potential donor will or will not expire in a time frame consistent with donation is extremely important, because prolonged time to asystole, likely resulting in suboptimal organ perfusion, is a common reason for non procurement of DCD grafts[48,49]. Time between therapy withdrawal and cardiac arrest usually does not exceed 1 h in most DCD donors. However, if a DCD donor has a period of relatively hemodynamic stability after life-support withdrawal, this period may be extended beyond 1 h without additional warm injury to the organs[50]. Some authors emphasized during the withdrawal phase, time to a systolic BP < 50 mmHg should be < 30 min[20] and the hypotensive period (mean BP < 50 mmHg) < 15 min[51]. Manara *et al*[52] proposed the so-called functional WIT, which is measured from the donor's systolic BP < 50 mmHg, the arterial oxygen saturation < 70%, or both, to the start of cold perfusion, should not exceed 30 min and may be limited to 20 min in suboptimal donors. Several factors have been identified as predictors of rapid death following treatment withdrawal and include the DCD tool of University of Wisconsin[53], donor Glasgow coma scale, inotropic use, BP at treatment discontinuation, high FiO2 and mode of ventilation[54,55]. Withdrawal of therapy is preferably occurred in the operating room with a donor surgical team immediately available. Prior to cessation of the ventilator and organ perfusion support, the donor may be already prepared and draped, and the surgical instruments, preservation solution and tubing are set up to facilitate rapid organ recovery. The super rapid recovery technique is preferable and organs may be removed *en bloc*[39,50]. For uncontrolled donors, *in vivo* organ preservation techniques, like in-situ intravascular cooling using a double balloon and triple lumen catheter or hypo- and normothermic cardiopulmonary bypass with extracorporeal membrane oxygenation (ECMO), should be employed. With regard to the logistic organization, two frequently mentioned initiatives are the "Maastricht's box" and the "Madrid's rapid identification and response system"[6].

Donor cause of death

DCD donors do not experience the brain dead process. Brain death provokes a cascade of changes in hemodynamics, hormones, and immune response, which negatively affect donor organ viability and transplant outcomes[56,57]. Hemodynamic instability may have deleterious effects on liver function, although the liver has a high tolerance to marked hypotension and a large physiological reserve. Only a few histological changes were observed in the liver both on light and electron microscopic examination during the brain dead process[58,59]. The most important changes are the increased liver immunogenicity with subsequent increased host alloresponsiveness and the occurrence of apoptosis of hepatocytes[60]. Clinical findings in livers from DBD donors revealed significantly higher leukocyte infiltrates, up-regulation of adhesion molecules [intercellular adhesion molecule (ICAM), vascular cell adhesion molecule] and pro-inflammatory cytokines [interleukin-6 (IL-6), IL-10, IL-1β, interferon γ and tumor necrosis factor-alpha (TNF-α)], along with an increased expression of major histo-compatibility complex-Ⅱ relative to livers from living donors[61,62]. The peak time of cytokine expression and cell infiltration is during brain death and organ procurement but not after reperfusion[61]. These changes may amplify ischemia-reperfusion injury (IRI) during the transplant procedure and accelerate graft rejection after transplant[63]. In reality, donor brain-death mechanisms are quite varied and large differences may exist in the degree of impaired organ quality and transplant outcomes. The impact of donor cause of death on transplant outcomes has been recently confirmed in a United Network for Organ Sharing (UNOS) registry analysis, in which the cerebro-vascular accident presented as a predictor of worse graft survival across all organs relative to other donor modes of death[64].

Uncontrolled DCD donors whose cause of death is usually other than neurologic do not undergo the process of brain death, while most controlled DCD donors have sustained irreversible cerebral injuries. As a result, organs from controlled DCD donors are likely to suffer more from the harmful immunologic and inflammatory effects of acute brain injury than those from uncontrolled DCD donors[65].

Allocation policy

It is reported that organs that have already subjected to warm ischemic injury have an increased susceptibility to damage during cold storage[66]. The incidence of primary non-function (PNF) was 2.5 times less in patients with

Table 1 Risk classification for donation after cardio-circulatory death donors and donation after cardio-circulatory death-liver transplantations recipients

Authors		Donors	Recipients
Mateo *et al*[74]	Low risk	Both WIT ⩽ 30 min and CIT ⩽ 10 h	RCRR ⩽ 1.5
	High risk	WIT > 30 min and/or CIT > 10 h	RCRR > 1.5 Re-transplantation and/or On life-support and/or A combination of ⩾ 3 risk factors: Hospitalization or in an intensive care unit Serum creatinine > 2 mg/dL On dialysis Age > 60 yr
Lee *et al*[32]	Low risk	Donors with no identified donor risk factors	Recipients with no identified recipient risk factors
	High risk	Donors with at least one identified donor risk factor: Donor age > 45 yr WIT > 15 min CIT > 10 h	Recipients with at least one identified recipient risk factor: Previous transplantation Life support at transplantation
de Vera *et al*[34]	Low risk	-	MELD scores ⩽ 30
	High risk	-	MELD scores > 30 On life support (mechanical ventilation, hemodialysis)

RCRR: Recipient cumulative relative risk; WIT: Warm ischemia time; CIT: Cold ischemic time; MELD: Model for end-stage liver disease.

cold ischemia time (CIT) ⩽ 8 h *vs* those with CIT > 8 h (5% *vs* 13%)[34]. The incidence of graft failure within 60 d of transplantation was 10.8% if CIT < 8 h and substantially increased to 30.4% and 58.3% if CIT > 8 h and > 12 h, respectively[67]. Proper and rapid allocation of DCD livers thus appears pivotal to minimize CIT. One-year graft survival of DCD livers shared regionally was less good than those shared locally (67% *vs* 77%)[68] and the relative risk of graft failure from nationally shared DCD livers was 31% higher than locally or regionally shared ones[69]. Thus a policy to favor local use of DCD livers seems reasonable[67,68]. However, parallel (backup) offers should also be made to expedite organ placement[33]. The exchange of DCD livers between transplant centers has been successfully done but requires a more efficient and rapid referral system due to a lower tolerance of these allografts to cold storage[70].

Regarding recipient selection criteria, DCD livers could be routinely discussed and offered to all recipients on the waiting list[20,70,71] or selectively reserved to uncomplicated cases to ensure short CIT (by avoiding cases with extensive history of abdominal surgery or portal-vein thrombosis)[20,35]. An expected long surgical procedure exceeding 8 h of CIT, logistical reasons for an extended CIT, combined organ transplantation, recipients with high Model for End-Stage Liver Disease (MELD) scores or a large age difference between donors and recipients could all result in the refusal of a DCD liver[51]. Patients with stable cholestatic liver disease or re-transplantation were also excluded from DCD programs because of problems related to the quality of life in primary biliary cirrhosis and to the fear that pre-existent warm ischemic biliary damage could trigger the recurrence of primary sclerosing cholangitis[72]. Using DCD livers in re-transplanted patients might increase the CIT associated with a difficult hepatectomy. Recently LaMattina has demonstrated the feasibility of simultaneous liver and kidney (SLK) transplantation using DCD donors and shown short-term results comparable to those of SLK transplantation using DBD donors, making it a valid approach to safely expanding the donor organ pool for patients with end-stage liver and kidney disease[73].

It is still controversial whether it is better to transplant such grafts into healthy or sicker recipients (i.e., according to the recipient liver disease severity). UNOS database reviews advocated utilizing DCD livers in "low-risk" recipients[32,67,74]. de Vera *et al*[34] also observed better graft survival when DCD livers were utilized in patients with MELD scores ⩽ 30, but simultaneously could demonstrate that "sicker", high-risk recipients (at MELD scores > 30 or on organ-perfusion support, like mechanic ventilation or hemodialysis) had a greater patient and graft survival benefit from the transplantation of DCD livers compared to patients who are not as critically ill. Risk classification for DCD donors and DCD-LT recipients is summarized in Table 1. Other groups of patients that may have a true survival benefit from DCD-LT include MELD "disadvantaged" patients (hepato-cellular carcinoma patients beyond the Milan criteria or who are listed in areas with long waiting times, patients with low MELD scores that do not adequately reflect their level of illness and their critical need for a transplant)[34,72].

Studies about the effect of DCD liver grafts on hepatitis-C virus positive (HCV+) recipients transplant outcomes were inconsistent. Nguyen *et al*[45] and recently Hernandez-Alejandro *et al*[75] found a negative effect of HCV on DCD livers, but a formal contraindication for the use of DCD liver allografts in HCV+ recipients was not justified except for older donors. In fact, while single-center series reported no significant difference in graft and patient survival rates of HCV+ recipients and graft loss from HCV recurrence between DCD and DBD groups[20,34,76,77], as well as no deleterious effects of DCD liver grafts on the disease progression (fibrosis)

in comparison with DBD liver grafts in HCV+ recipients[77], the most recent UNOS registry data showed inferior graft survival but similar patient survival of HCV+ recipients with DCD donors compared to ones with DBD donors. Furthermore, DCD livers on HCV disease do not fare worse than DCD livers on non-HCV disease. DCD livers thus appeared to be important source of LT for HCV patients[78]. Split livers from DCD donors have also been reported in recent years with acceptable results[79,80].

TRANSPLANT OUTCOMES

Currently one-year patient survival after DBD-LT and to a certain extent after controlled DCD-LT is about 85%-90% in comparison to 60% in the early eighties and around 30% in the early d of LT and at 5 years post-transplant patient survival rate remains over 70%. Medical progress over the past 40 years in the field of organ preservation, surgical techniques, immunosuppressive drugs, treatment of post-transplant complications and organ allocation has permitted DCD to become reality in the modern era. Although there are concerns about the quality of such organs, with evidence that a prolonged WIT causes a raised incidence of PNF and biliary complications as well as suboptimal graft and patient survival when compared to DBD livers, DCD livers may be life-saving for those who would die waiting for a DBD liver[68] and do increase the number of organs available for LT. With careful donor/recipient selection and matching, minimization of ischemia and good post-operative care, acceptable results can be achieved. Essential results of most important publications in the last decade in DCD-LT are presented in Tables 2-4.

Primary non-function

PNF is usually defined as unrecoverable hepato-cellular dysfunction leading to patient death or re-transplantation within the first week post-transplant after excluding other causes of graft failure such as vascular thrombosis, biliary complications, rejection or recurrent disease[81-84]. Initial studies using uncontrolled DCD donors reported a rate of PNF as high as 50%[85]. Currently only a few transplant centers in the world (like Spain, France) used this kind of donors because of aforementioned reasons. By using different *in vivo* organ preservation methods to maintain DCD donors and by strictly applying donor selection criteria, authors in Madrid[71], Barcelona[29] and La Coruña[86-89] could obtain promising results from Maastricht category I and II donors with a PNF rate of 10%-25%. The discard rate nevertheless was high up to 50%-75%[29,71]. In controlled DCD donors, the PNF rates are 0% to 12%. Matched analysis[34,72] and registry data[67,68] showed a higher rate of PNF in controlled DCD than DBD donors, although no difference was found in most comparative studies[20,43,90,91] except one[92]. The increased risk of PNF in DCD-LT recipients was also confirmed in a recent meta-analysis (odds ratio = 3.6, 95% CI: 2.1-6.4)[93]. Case-series reports of controlled DCD-LT also had a rate of PNF between 0% and 10%[42,70,94-97].

PNF is the consequence of severe IRI with the initial period of warm ischemia playing a crucial role. Experimental evidence supported that donor WIT should be less than 30 min to minimize PNF[98]. This warm ischemia (WI) period increases graft susceptibility to damage during cold preservation and CIT was a main contributing factor to PNF[34,67]; therefore, both periods of ischemia must be kept to a minimum. Many laboratory tests have been developed both in animal models and in human to predict the probability of occurrence of PNF post-transplant, but none is yet clinically efficient[99]. Recently Dahaba proposed bispectral index monitoring as an early intra-operative indicator of early graft dysfunction[100].

Biliary complications

Since the introduction of LT up to now, biliary complications are always regarded as the "Achilles heel" and a major cause of morbidity and graft failure in patients after LT[101]. The most common biliary complications are bile leakage and bile duct stricture[102,103]. Strictures involving the donor bile duct (> 1 cm above the biliary anastomosis) and requiring endoscopic or radiological dilatation/stenting or surgery in the face of a patent, non-stenotic hepatic artery was referred to as ischemic-type biliary lesions (ITBL), based on the radiologic resemblance of those occurring after hepatic artery thrombosis (HAT)[51,91,103].

Abt *et al*[104] first mentioned the significantly higher incidences of overall biliary complications as well as ITBL in DCD-LT recipients, the finding which was later confirmed in both matched[34,72] and comparative[20,43,51,89,91,104] studies except series of Fujita *et al*[105] and Manzarbeitia *et al*[106]. The rates of overall biliary complications and ITBL were 10.5%- 53% and 8.3%-38%, respectively in DCD-LT compared to 8.3%-22% and 0%-8%, respectively in DBD-LT. Especially Jimenez-Galanes reported only a 5% incidence of ITBL in their patients receiving livers from uncontrolled DCD donors under normothermic ECMO[71]. A recent meta-analysis revealed that DCD recipients had a 2.4 times increased odds of biliary complications (95% CI: 1.8-3.4) and a 10.8 times increased odds of ITBL (95% CI: 4.8-24.2) *vs* DBD recipients. In average, biliary complications were present in 29% of DCD compared with 17% of DBD recipients and ITBL in 16% of DCD *vs* 3% of DBD recipients[93].

Furthermore DCD recipients who developed ITBL experienced a fairly rapid clinical deterioration, characterized by a relatively short mean time from transplant to first endoscopic retrograde percutaneous cholangiopancreatography (ERCP), from first ERCP to relisting and from relisting to re-transplantation (within 180 d)[36,69]. ITBL results in re-operation, multiple endoscopic and percutaneous biliary interventions, re-transplantation and even patient death with markedly increased medical care costs[107]. The relative risk (RR) of developing graft

Table 2 Results of donation after cardio-circulatory death-liver transplantations in single-center studies

Authors study period	Transplant center	Publication year	Patient number and Maastricht category	WIT (min)	CIT (min)	Mean follow-up	PNF %	Major biliary complications %	ITBL %	HAT %	HAS %	Rejection %	Retransplantation %	Graft survival %				Patient survival %			
														1 yr	3 yr	5 yr	10 yr	1 yr	3 yr	5 yr	10 yr
Casavilla *et al*[85]	Pittsburgh,	1995	6 DCD_4	37	10.6 h	-	50[1]	-	-	16.6	-	-	83.3	17	-	-	-	67	-	-	-
1989-1993	United States		6 DCDc	23.8	11 h	-	0[1]	-	-	33.3			33.3	50	-	-	-	50	-	-	-
Otero *et al*[87]	Madrid, Spain	2003	20 DCD_2	10	647	> 2 yr	25[1]	30[1]	-	0	-	27	25	80	-	-	-	80	-	-	-
1995-2000			40 DBD	8	405	-	3[1]	8[1]				34	5	55	-	-	-	83	-	-	-
Quintela *et al*[86]	Spain	2005	9 DCD_2 + 1 DCD_4	80	561	-	10	-	-	-	-	-	10	100	-	-	-	100	-	-	-
1995-2004																					
Suárez *et al*[89]	Spain	2008	27 DCD_2	13	635	> 3 mo	18[1]	41.7[1]	25.0[1]	3.6	-	17.4	-	-	-	49[1]	-	-	-	62	-
1994-2005			471 DBD	7	-	-	3[1]	16.8[1]	2.3[1]	3.1	-	28.6				68[1]	-	-	-	74	-
Fondevila *et al*[29]	Barcelona, Spain	2007	10 DCD_1	-	399	-	10	10	-	10	-	-	20	50	-	-	-	70	-	-	-
2002-2006			20 DBD	-	-	-	0	0	-	5	-	-	5	75	-	-	-	80	-	-	-
Jiménez-Galanes *et al*[71]	Madrid, Spain	2009	20 DCD_2	12	432	360 d	10	5	50	0	-	-	1[1]	80	-	-	-	85.5	-	-	-
2006-2008			40 DBD	6	409	-	2.5	-	-	-	-	-	50[1]	87.5	-	-	-	87.5	-	-	-
Pine *et al*[72]	St. James, London,	2009	39 DCDc	13.4	352	2.5 yr	5.1	33.3[1]	20.5[1]	2.6	12.8[1]	20.5	7.6[1]	79.5[1]	63.6[1]	-	-	80[1]	68.2[1]	-	-
2002-2008	United Kingdom		39 DBD	-	593	6.6 yr	-	10.2[1]	-	5.1	-	23.1	2.5[1]	97.4[1]	97.4[1]	-	-	100[1]	1[1]	-	-
de Vera *et al*[34]	Pittsburgh,	2009	141 DCDc	19.8	657	-	12[1]	25[1]	16.3[1]	66	-	-	18[1]	69[1]	-	56[1]	44[1]	79	-	70	57
1993-2007	United States		282 DBD	-	636		3[1]	13[1]	< 1[1]	-	-	-	7[1]	82[1]	-	73[1]	63[1]	85	-	76	64
Yamamoto *et al*[90]	Stockholm, Sweden	2010	24 DCDc	6	7 h	> 20 yr	8.3	37.5[1]	-	33.3[1]	-	70.8	-	54.2	-	37.5	37.5	61.9	-	42.9	42.9
1984-1988			16 DBD	-	6.8 h	> 20 yr	18.7	6.3[1]	-	-	-	56.2	-	43.8	-	37.5	37.5	63.6	-	-	54.5
Fujita *et al*[105]	Gainesville, Floria,	2007	24 DCDc	12.8	7.6 h	-	2.8	25	12.5	8.3	-	39.1	20.8	69.1	58.6	-	-	86.8	81.7	-	-
1990-2006	United States		1209 DBD	-	8.1 h			20.5	-	4.1	-	-	9.4	78.7	70.2	-	-	84	76	-	-
Foley *et al*[91]	Wisconsin,	2005	36 DCDc	17.8	8.2 h	3 yr	5.5	33[1]	13.8	5.5	16.6[1]	61	19.4[1]	67[1]	56[1]	-	-	80[1]	68[1]	-	-
1993-2002	United States		553 DBD	-	8.3 h	4.6 yr	1.3	10[1]	8	11.8	5.4[1]	56	7[1]	86[1]	80[1]	-	-	91[1]	84[1]	-	-
Manzarbeitia *et al*[106]	Philadelphia,	2004	19 DCDc	19.6	574	1000 d	5.2	10.5	-	-	-	-	10.5	-	-	-	-	89.5	-	-	-
1995-2002	United States		311 DBD	-	557	-	-	13.8				-	8.7	-	-	-	-	84.2	-	-	
Abt *et al*[104]	Pennsylvania,	2003	15 DCDc	20.4	366	819 d	6.7	33.3[1]	26.7[1]	3.2	-	20	6.6[1]	71.8	71.8	-	-	79	79	-	-
1996-2001	United States		221 DBD	-	464	690 d	3.6	9.5[1]	2.3[1]			21.3	3.6[1]	85.4	73.9			90.9	77.7		
Nguyen *et al*[45]	Mayo Clinic, Floria,	2009	19 DCDc	16	6.7 h	> 4.5 yr	5.3	26.3	10.5	0	5.3	5.3[1]	15.8	73.7	68.4	63.2	-	89.5	89.5	89.5	-
1998-2001	United States		234 ECD	-	7.1 h	-	4.7	22.6	-		-	33.3[1]	8.5[1]	-	-	-	-	85	78.6	72.3	
			214 SCD	-	7.5 h	-	1.7	15.9	-		-	33.2[1]	19.6[1]	-	-	-	-	84.3	80.7	76.5	

DCDc: Controlled donors after cardiac death; DCD_1, DCD_2 and DCD_4: Maastricht category-1, category-2 and category-4 DCD donors; DBD: Donors after brain death; SCD: Standard criteria donors; ECD: Extended criteria donors; WIT: Warm ischemia time; CIT: Cold ischemia time; PNF: Primary non-function; ITBL: Ischemic-type biliary lesions; HAT: Early hepatic artery thrombosis; HAS: Early hepatic artery stenosis. Major symptomatic biliary complications include biliary leak, anastomotic and non-anastomotic stenosis. [1]Numbers denote the statistically significant difference between groups.

loss with ITBL formation was 3.02 (95% CI: 1.9-5.3) and graft survival was significantly decreased in patients with non-anastomotic strictures, compared to patients without it[89]. Up to 50% of all occurrences of ITBL lead to death and/or re-transplantation[108].

ITBL is usually a reflection of severe IRI in relation to various factors. In animal models, irreversible biliary tract damage has been observed after 40 min of cardiac arrest although hepato-cellular function could be preserved[109]. Clinical observations showed that total WIT > 30 min and chaotic donor physiology before asytole may increase the risk of post-transplant biliary stricture[33,110]. The mechanism could come from the stasis of blood and clot formation in the peri-biliary micro-circulation whose blood is solely supplied by the hepatic artery[96]. Many multivariate analysis recognized DCD liver grafts as an independent risk factor for the appearance of ITBL (RR = 47.1)[51,89].

Table 3 Results of donation after cardio-circulatory death- liver transplantations in single-center studies

Authors study period	Transplant center	Publication year	Patient number and Maastricht category	WIT (min)	CIT (min)	Mean follow-up	PNF %	Major biliary complications %	ITBL %	HAT %	HAS %	Rejection %	Retransplantation %	Graft survival %			Patient survival %		
														1 yr	3 yr	5 yr	1 yr	3 yr	5 yr
Grewal *et al*[20]	Mayo Clinic, Floria,	2009	108 DCDc	22.3	6.3 h		3.7	-	8.3[1]	0.9	-	-	14.8	79.3	74.5	71	91.5	88.1	88.1
1998-2006	United States		1328 DBD		7.1 h		1.4		1.9[1]	1.7			9.3	81.6	74.7	69.1	87.3	81.1	77.2
Kaczmarek *et al*[41]		2007	11 DCDc	34.6	7.6 h	> 14 mo	0	45.4[1]	1[1]	0	-	-	9.1[1]	-	-	-	-	-	-
1999-2006			164 DBD		-		-	16.4[1]	8.2[1]	-			0[1]						
Dubbeld *et al*[51]		2010	55 DCDc	16.5	456	-	2	28[1]	24[1]	74.7	-	-	18	74	68	-	85	80	-
2001-2006			471 DBD		515		1.5	8.3[1]	7.9[1]				10.4	80.4	74.5		86.3	80.8	
Chan *et al*[43]	Seattle, United States	2008	51 DCDc	-	-	3 yr	0	23.5[1]	13.7[1]	4.8	-	-	9.8	79	79	-	83	83	-
2003-2006			334 DBD			-	3.3	8.9[1]	1.2[1]				-	85	77		88	78	
Skaro *et al*[36]	Chicago, United States	2009	32 DCDc	15.8	5.5 h	-	3	53[1]	38[1]	93	-	-	2[1]	61[1]	53[1]	-	74	74	-
2003-2008			237 DBD		5.2 h		1	22[1]	2[1]				27[1]	85[1]	74[1]		90	81	
Jay *et al*[107]	Chicago, United States	2010	28 DCDc	16.5	5.7 h	1.8 yr	3.6	57.7[1]	44[1]	10.7	7.1	-	21.4[1]	60[1]	50[1]	-	70[1]	70[1]	-
2004-2008			198 DBD		5.3 h	-	0.5	21[1]	1.6[1]	3	6.1		7.1[1]	89[1]	78[1]		96[1]	93[1]	
Dezza *et al*[92]	Ghent, Belgium	2007	13 DCDc	10	6.16 h	163 d	8[1]	-	23.1[1]	-	-	-	31[1]	54[1]	-	-	62[1]	-	-
2003 -2006			98 DBD		9.14 h	603 d	1[1]		-				12[1]	79[1]			86[1]		
Maheshwari *et al*[95]	Johns Hopkins Balti-		20 DCDc	33	8.7 h		5	60	50	5	-	-	20	62	62	30	78	78	40
1997-2006	more, United States																		
Muiesan *et al*[70]	London,	2005	31 DCDc	14.7	8.6 h		3.1	9.4	0	3.1	-	28.1	3.1	86.5	-	-	89.6	-	-
2001-2004	United Kingdom																		
Abou Abbass *et al*[97]	United States	2010	26 DCDc	39	5.3 h		0	46	15.4	11.5	7.7	26.9	23	77	-	-	92	-	-
2004-2008																			
Detry *et al*[94]		2010	58 DCDc	25	451		3.4	38	32.7	3.4	3.4	-	13.8	72.4	48.8	-	83.3	66.9	-
2003-2007																			
Hernandez-Alejandro *et al*[42]	London,	2010	10 DCDc	54.7	5.8 h		10	10	0	0	0	-	10	-	-	-	-	-	-
2006-2007	United Kingdom																		
Hashimoto *et al*[96]	United States	2010	22 DCDc	21	422		4.5	27	9	0	0	-	9	81	81	-	-	-	-
2005-2009																			

DCDc: Controlled donors after cardiac death; DBD: Donors after brain death; SCD: Standard criteria donors; ECD: Extended criteria donors; WIT: Warm ischemia time; CIT: Cold ischemia time; PNF: Primary non-function; ITBL: Ischemic-type biliary lesions; HAT: Early hepatic artery thrombosis; HAS: Early hepatic artery stenosis. Major symptomatic biliary complications include biliary leak, anastomotic and non-anastomotic stenosis. [1]Numbers denote the statistically significant difference between groups.

Biliary epithelium is also known to be sensitive to cold preservation-reperfusion injury and the correlation between the incidence of ITBL and the duration of cold ischemia has been well documented. Li *et al*[111] demonstrated that the rate of ITBL is significantly increased in livers with increased preservation injury, as reflected by post-transplant peaks in serum transaminases. Other variables implicating in the mechanisms of ITBL may include injury of the peri-biliary vascular plexus, bile salt toxicity and potential immunological etiologies (ABO incompatibility, liver diseases with autoimmune component like autoimmune hepatitis and primary sclerosing cholangitis)[102]. Chan *et al*[43] found donor age > 50 years, donor weight ≥ 100 kg and total ischemia time ≥ 9 h were predictive for the development of ITBL. Patients who underwent LT from DCD donors > 60 years had a markedly high rate of biliary complications (67%), with a RR of 5.6 (95% CI: 0.98-32.2)[34].

Due to serious consequences of ITBL on the patient's quality of life and healthcare cost, preventive measures seem to play a pivotal role in the safe expansion of DCD liver use. Attempts to minimize biliary duct damage may include the use of normothermic ECMO for donor maintenance[29,71,112] and machine perfusion for liver grafts, choice of preservation solutions [histidine-tryptophan-ketoglutarate (HTK) *vs* University of Wisconsin][113-117], use of anticoagulation and thrombolytic agents[96], extensive

Table 4 Results of donation after cardio-circulatory death-liver transplantations in United Network for Organ Sharing data base registry

Authors and study period	Publication year	Patient number and Maastricht category	WIT (min)	CIT (h)	PNF (%)	Retransplantation (%)	Graft survival %			Patient survival %		
							1 yr	3 yr	5 yr	1 yr	3 yr	5 yr
Abt *et al*[67]	2004	144 DCD	12.7	8.1	11.8[1]	13.9[1]	70.2[1]	63.3[1]	-	79.7	72.1	-
1993-2001		26 856 DBD		8.9	6.4[1]	8.3[1]	80.4[1]	72.1[1]		85	77.4	
Mateo *et al*[74]	2006	367 DCD	15.6	8.3	-	-	71[1]	60[1]	53[1]	-	-	-
1996-2003		33 111 DBD		8.4			80[1]	72[1]	65[1]			
Lee *et al*[32]	2006	874 DCD	15.4	7.9	-	-	72.1[1]	61.8[1]	38.8[1]	82.3[1]	75.9[1]	65.3[1]
1996-2006		43 734 DBD		8.2			80.7[1]	71.9[1]	65.6[1]	85.4[1]	77.5[1]	71.5[1]
Doshi *et al*[68]	2007	345 DCD	-	8.2	6.4[1]	13.0[1]	75	65	-	83	77	-
1998-2004		20 289 young-DBD		8.1	3.9[1]	5.6[1]	83[1]	75[1]		88[1]	80[1]	
		3604 old-DBD		8.2	5.3[1]		76	64		83	73	
Merion *et al*[125]	2006	472 DCD	-	7.9	-	-	70.1[1]	60.5[1]	-	-	-	-
2000-2004		23 598 DBD		8.1			83[1]	75[1]				
Selck *et al*[69]	2008	855 DCD	-	-	-	21.6[1]	73.8[1]	57.6[1]	-	-	-	-
2002-2007		21 089 DBD				8.8[1]	84.4[1]	74.4[1]				
Mathur *et al*[127]	2010	1567 DCD	16.1	7.5	-	13.6	-	-	-	78	64.9	-
2001-2009												

DCD: Donors after cardiac death; DBD: Donors after brain death; WIT: Warm ischemia time; CIT: Cold ischemia time; PNF: Primary non-function. Major symptomatic biliary complications include biliary leak, anastomotic and non-anastomotic stenosis. [1]Numbers denote the statistically significant difference between groups.

irrigation of the donor bile duct and pressure perfusion of the hepatic artery during organ retrieval and/or at back table[113,118,119], early porto-caval shunt to reduce portal hypertension in the recipient, choice of reperfusion techniques (concomitant *vs* sequential reperfusion of portal vein and hepatic artery)[120] and certainly the most important thing is always minimizing warm and cold ischemia period[121].

HAT and stenosis

HAT is a thrombo-embolic occlusion of the hepatic artery that can occur early or late after LT. Most authors used the first 30 d post-transplant as a time point to distinguish between early and late HAT[122]. Early HAT results in fulminant hepatic failure, bile duct necrosis and leaks, relapsing bacteremia and ultimately graft loss and recipient death. The frequencies of early HAT after DCD-LT varied from 0% to 16.6% and did not seem significantly higher than those after DBD-LT in most studies[20,29,34,36,43,51,71,72,89,91,104,105] except Yamamoto *et al*[90] (33.3% *vs* 0%). Risk factors for early HAT have been well analyzed in a recent systemic review[123]. Few detailed studies discussed late HAT.

The incidence of hepatic artery stenosis (HAS) was not consistently found higher in DCD than DBD grafts (12.8%-16.6% *vs* 0%-5.4%)[72,91]. It is possible that hepatic arteries are susceptible to WI during DCD organ retrieval, resulting in subsequent scar and stenosis. Moreover the increased susceptibility of DCD livers to post-operative arterial ischemia might be responsible for more biliary strictures in DCD than DBD recipients with HAS (83% *vs* 37%) as well as shorter time to the development of biliary strictures after HAS in the DCD group[91]. Inadequate surgical technique, vascular trauma by clamps, graft rejection, recurrent hepatic disease might also play a role in the mechanisms for HAS[72,124].

Graft and patient survival

Graft survival is defined as the time from transplantation to either re-transplantation or patient death, with "early" and "late" graft failure occurring within and beyond 1 year post-transplant, respectively[34]. Few studies reported experience with LT from uncontrolled DCD donors. Early results were poor with a PNF rate of 50% and one-year graft survival rate of only 17%[85] leading to a scarce usage of this donor category in the United States. Subsequent series in Spain using advanced *in vivo* organ preservation methods showed promising outcomes with one- and five-year graft survival rates of 50%-80% and 49%, and one- and five-year patient survival rates of 70%-85.5% and 62%, respectively[29,71,89]. LT from controlled DCD donors offered better results although they still appeared inferior to DBD-LT in matched studies[34,72], registry data analysis[32,67-69,74,125] and in some comparative studies[36,91,92]. One-, three-, five- and ten-year graft survival rates were 54%-79.5%, 53%-74.5%, 37.5%-71% and 37.5%-44%, respectively. Patient survival rates at corresponding time points were 61.9%-91.5%, 62.8%-89.5%, 42.9%-89.5% and 42.9%-57%, respectively. Transplant outcomes comparable to those obtained from DBD-LT have been sporadically reported in select centers through careful donor selection and optimization of CIT or through invasive techniques designed to optimize recovery before declaration of death[20,43,51,104].

Significant risk factors for DCD liver graft loss have been identified by multivariate Cox regression technique in both single center studies and large data registry analysis[32,67-69,74,126,127]. Among donor risk factors, age > 50 years, total WIT > 30-35 min, CIT > 6 h, body weight > 100 kg and regional or national liver distribution had deleterious effects on graft survival[32,74,127]. There is a stepwise increase in the relative risk of graft failure among donor age, WIT and CIT[32,127]. Strong recipient determinants of

graft failure include age > 55 years, history of previous transplantation, medical status at transplantation [intensive care unit (ICU) or non-ICU hospitalization, life support, dialysis, renal insufficiency], high MELD score (> 30) and positive HCV serology[32,74,127]. In the DBD-LT model, it has been shown that a single risk factor lessened outcome marginally, however, the additive effect of multiple risk factors in a given donor-recipient pair were disastrous[83]. Grafts with ≥ 3 donor risk factors had significantly lower 1-year post-transplant survival than no or only 1 or 2 risk factors (58.3% *vs* 72.6%, 69.2% and 73.9%, respectively). No grafts with 4 risk factors survived within 1 year[128]. The relative risk of allograft failure from LT utilizing DCD donors was 31%-87% higher than LT utilizing DBD donors[67-69,125,126]. Causes of early graft failure included PNF, biliary complications, HAT and deaths from sepsis/multi-organ failure. Late graft failure was often secondary to chronic rejection and recipient death with a functioning graft.

Although DCD livers may not be as good as DBD ones with potential inferior transplant outcomes, there are subgroups of grafts and recipients that could give favorable results through appropriate graft and recipient matching. Low-risk DCD grafts which are transplanted in low-risk patients lead to comparable graft survival rates with DBD livers. Livers from DCD donors transplanted into high-risk recipients fared poorly independent of the allograft quality[74]. Doshi *et al*[68] showed DCD liver grafts were not inferior to DBD livers from older donors (≥ 60 years). Given the ever increasing demand for LT, DCD livers appear to be a reasonable alternative to increasing use of older or split livers and are a reasonable option when death is imminent[68]. Even if graft or/and patient survival is lower with a DCD liver, it is still better than dying because of turning down a DCD offer and continuing to wait for a DBD liver on these d as the patient' s choice is frequently not between marginal livers (including DCD) and standard livers but between marginal livers and no livers[105]. The benefit of earlier access to LT provided by a DCD graft could outweigh the risks of prolonged waiting for a standard graft[77].

Re-transplantation

DCD recipients more often require re-transplantation. Respectively, 21.6%-42% *vs* 8.8%-16% of DCD and DBD recipients were listed for re-transplantation[36,69]. The re-transplantation rate ranged from 7.6% to 31% in DCD-LT compared to 2.5%-12% in DBD-LT[20,29,34,36,51,67-69,71,72,91,92,106]. DCD livers exhibited a 2.1 times greater risk of graft failure, a 2.5 times greater risk of re-listing, and a 3.2 times greater risk of re-transplantation compared with DBD livers[36]. The majority of re-listing and re-transplantation in the DCD group were a consequence of biliary complications, especially ischemic cholangiography, but not due to an increased incidence of PNF, HAT or technical complications[36,69]. Particularly DCD livers had a temporally different failure pattern within the first year post-transplant that limited access to re-transplantation[36,69]: graft failure was more likely to occur within the first 180 d (18.1% *vs* 11.7%[67], 10.2% *vs* 2.5%[72] and 20.5% *vs* 11.5%[69] of DCD and DBD grafts failed within 60, 90 and 180 d, respectively); at re-transplantation, DCD recipients waited longer and received higher risk allografts; and more DCD recipients remained waiting for re-transplantation with fewer removed for death, clinical deterioration, or improvement. Re-transplantation arouses controversy on medical, economic, and ethical grounds: patient and graft survival rates after a second LT are inferior to those after initial grafting, the procedure is more expensive and in the context of organ shortage, re-transplantation inevitably denies organs to first-time recipients[129].

Utilization of DCD allografts for re-transplantation was rare (2.5% of initial DCD *vs* 3.1% of initial DBD) and outcomes from each group were comparable[69]. The general practice is to avoid re-transplantation with a DCD graft[36]. The use of DCD donors in the setting of re-transplantation resulted in an increased risk of recipient death (hazard ratio = 2.1, 95% CI: 1.2-3.6)[129].

Acute rejection

The acute rejection rate did not differ significantly between DCD- and DBD-LT in most studies (1.9%-29% *vs* 0.6%-34%)[20,72,87,89,104]. Foley *et al*[91] reported a one-year rejection rate of 61% in the DCD group similar to that in the DBD group (56%). There were little data looking at the impact of DCD source on the risk of acute rejection.

EXPERIMENTAL STRATEGIES TO IMPROVE DCD-LT OUTCOMES

The progressively increased DCD liver procurement to solve the shortage of DBD organs and to alleviate the waiting-list mortality has raised many challenges to the transplant community and transplant policy makers[110]. A lot of experimental researches have been performed over the past decade, intervening in both donors and recipients at different phases of the transplantation process, at the aim of tackling some of these challenges and providing a deep insight into IRI mechanisms.

Donor pre-treatment

Various cyto-protective substances have been successfully administered into the donor prior to cardiac arrest for prevention of liver microcirculatory disturbance. Microcirculatory disturbance was the main obstacle to successful DCD-LT, which was due to four major mechanisms: deterioration of sinusoidal endothelial cells (SEC) caused by activated Kupffer cells, sinusoidal narrowing caused by some vasoconstrictors and swollen hepatocytes, leukocyte and platelet adhesion, and hyper-coagulability[130]. Up to now, only *Heparin* and *phentolamin* (an anticoagulative substance and alpha-adrenergic antagonist) are allowed in clinical DCD organ procurement[131], other substances remain in animal models. *Tacrolimus,* besides

its powerful immunosuppression, enabled to prevent liver normothermic IRI by multiple mechanisms[132]. *Milrinone*, a type 3 phosphodiesterase inhibitor, attenuated graft injury caused by warm and cold ischemia *via* an increase in intracellular cAMP levels, protection of SEC, relaxation of hepatic stellate cells, inhibition of platelet aggregation and anti-inflammatory effect[133]. *Lazaroids*, an antioxidant designed to inhibit iron-dependent lipid peroxidation, ameliorated SEC viability *via* antioxidant effects and membrane stabilization[134]. *N-acetylcystein* has a direct effect on oxygen free radicals, but its usage had no effect in both graft viability and lipid peroxidation[135].

Animal studies clearly showed the concept of pharmacological modulation of organ donors before procurement is feasible to improve the viability of marginal grafts. Nevertheless there are no definitive recommendations for the use of these drugs. Application of this method to clinical LT would require management of some practical problems and possible ethical conflicts[136].

Organ preservation

Preservation of DCD livers by hypothermic machine perfusion (HMP) was shown superior to static cold storage (SCS) in many experimental studies[137,138].

Nonetheless a putative drawback of HMP for livers is to induce alterations at the vascular endothelial site, especially if HMP was performed for a long time or under suboptimal conditions[139]. Endoplasmic stress activation promoted cellular apoptosis *via* activation of caspase-12[140,141]. The efficiency of HMP was markedly increased by oxygenation of the perfusate[142]. The concern that high oxygenation might favor the generation of oxygen free radicals, which in turn could impair tissue integrity, was not justified. Several investigators could demonstrate the beneficial effect of oxygenated HMP in reducing the liver expression of pro-inflammatory cytokines (TNF-α, IL-8), adhesion molecules (ICAM-1) and major histocompatibility complex class Ⅱ antigens[143-145]. This benefit will likely be more pronounced in marginal grafts such as elderly, steatotic and DCD livers[144]. Cyto-protective agents can be added into the machine perfusion (MP) solution to ameliorate the efficiency of HMP organ preservation[146].

The positive effects of HMP on warm-ischemically pre-damaged livers were observed even after a brief period of MP, before (pre-conditioning) or after SCS (post-conditioning)[143,147] and therefore it was not necessary to require MP over a full preservation period and helped avoid side-effects of HMP on vascular endothelium[141]. The use of HMP as the initial method for organ preservation followed by secondary SCS during transportation combined the advantage of aerobic resuscitation (i.e., restitution of cellular homeostasis) with an ease of SCS for later surveillance and transportation[141]. Manekeller showed a post-conditioning of 1 h after SCS can ameliorate the viability of marginal livers. The extension or abbreviation of post-conditioning time seems to have no further beneficial effects[148].

Schön *et al*[66] reported advantages of normothermic machine perfusion (NMP) over SCS in pig DCD-LT models. Livers subjected to 1 h of WI and then cold-stored for 4-24 h were rendered completely nonviable while such livers under 4-24 h of oxygenated NMP recovered function to a viable level[149]. Due to the complexity of the logistics of clinical multi-organ recovery and of the NMP device, a period of cold preservation prior to warm perfusion of the liver is unescapable. A brief period of cold preservation (1 h) prior to NMP could maintain the synthetic and metabolic function but resulted in significant hepatocellular damage, sinusoidal endothelial cell dysfunction and Kupffer cell injury[150]. Once this duration was prolonged to 4 h, NMP completely failed to resuscitate porcine livers[151]. Normothermically perfusing DCD livers throughout the preservation period not only replenished cellular substrate, ameliorating the ischemic injury, but also provided a clear assessment of liver function and therefore could permit the use of severely injured organs with reassurance of function[149,152].

Despite the aforementioned benefits of MP over SCS in liver preservation, only SCS is clinically approved up to now, MP is still in the pre-clinical stage and early clinical studies[153]. Tojimbara showed the impact of viscosity and temperature of initial flushing solutions on graft function. A low viscosity flushing solution was associated with lower vascular resistance, whereas a warm flush solution prevented cold-induced vasospasm and therefore improved the washout effect of the microcirculation[154]. HTK solution possessing a low viscosity and low potassium is more preferable in the DCD setting. The role of aeration of the cold-stored liver was also clarified. Oxygen provided either by surface diffusion (surface oxygenation) or intravascular diffusion (oxygen persufflation) helps improve the energy status of organs thus leading to earlier recovery. Surface oxygenation was not in use any more due to complicated technique, limited efficiency and risk of oxygen intoxication[155]. Venous systemic oxygen persufflation (VSOP) was shown to improve organ viability during hypothermic storage of the grafts and to be a feasible means for reconditioning of warm-ischemically pre-injured livers from DCD donors[155-158]. Experimentally even a short period of VSOP prior to long-term preservation of the liver by SCS may be sufficient for a relevant improvement of liver integrity upon reperfusion[159]. Gaseous persufflation with carbon monoxide was also tested in a DCD-LT rat model with enhanced liver graft viability[160]. However no additive or synergistic effect was noted when livers were persufflated with a mixture of gaseous oxygen and carbon monoxide[161].

Pharmaceutical interventions during SCS aimed at conditioning marginal organs also increasingly gained attention. Different cyto-protective drugs have been added into the flush and/or preservation solution, like vasodilators (phentolamin, epoprosterol, dopamine)[162,163], anti-coagulants (heparin), fibrinolytic agents (strepto-

kinase)[164], antioxydants (superoxide dismutase, edaravone)[165,166], antibiotics, hormones (glucagon, growth factors)[167]. In the DCD setting, vasodilators, anti-coagulants, thrombolytic agents and antibiotics seem particularly necessary because the organs tend to develop vasospasm, thrombus formation in the microcirculation and the risk of colonic bacterial contamination secondary to translocation of organisms during the WI period[168,169].

Viability testing

Due to serious consequences of transplanting a DCD liver with potentially severe IRI (PNF, re-transplantation or even recipient death), it would be ideal if the viability of such livers could be predicted prior to rather than after transplantation. WIT is not always exactly known and thus cannot be a reliable parameter. Light microscopic examination of biopsy specimens was unable to uniformly predict liver function after transplantation[170]. Monbaliu showed the extent of parenchyma vacuolation predicted pig liver graft viability before LT[171]. Muiesan *et al*[70] applied the mechanical digestion of liver biopsies with collagenase and assessed the viability of hepatocytes by trypan blue exclusion method. However, the test was not helpful and the decision as to whether to use the liver was generally made on gross appearance, ease of perfusion, degree of steatosis and donor characteristics[172].

Another approach is to evaluate the vascular resistance and enzyme release in the perfusate of HMP livers. Resistance index of the portal vein and hepatic artery showed no utility[173]. Biomarkers of liver cell damage, like transaminases, lactate dehydrogenase and liver fatty acid binding protein, correlated well with WI duration and concomitant hepatocyte damage in pig DCD-LT models[174]. Possible other parameters are the ATP content and redox active iron status of the liver during HMP[175]. During NMP, the assessment of liver viability may be easier because the liver is in a normal metabolic state. Bile production was a good viability indicator besides the measurement of other liver functions (detoxification, metabolism or synthesis)[176]. Recently Liu *et al*[177] has tested the utility of magnetic resonance imaging and proton magnetic resonance spectroscopy to evaluate WI livers without success.

Recipient treatment

Pharmaceutical strategies aimed at modulating IRI mechanisms were also applied successfully in animal recipients and generally did not impose ethical problems as donor pre-treatment. Such protocols without donor pretreatment will be favorable in clinical application. Most studies tested a single agent for a specific target of the IRI process. A multi-factorial approach acting on different pathways of the IRI process have been advocated and remarkably ameliorated transplant outcomes[162].

PERSPECTIVES

The future of DCD-LT is promising. Concerted efforts should concentrate on the identification of suitable donors (probably Maastricht category Ⅲ DCD donors), better donor and recipient matching (high risk donors to low risk recipients), use of advanced organ preservation techniques (oxygenated HMP and NMP, VSOP), and pharmacological modulation (probably a multi-factorial biologic modulation strategy) so that liver procurement and transplantation from DCD donors could be widely expanded and attain equivalent results as DBD-LT.

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