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REVIEW

Liver transplantation with grafts obtained after cardiac death-current advances in mastering the challenge

Fateh Bazerbachi, Nazia Selzner, John B Seal, Markus Selzner

Fateh Bazerbachi, Department of Medicine, University of Minnesota, Minnesota 55455, United States
Nazia Selzner, Department of Medicine, University of Toronto, Multiorgan Transplant Program, Toronto General Hospital, ON M5G 2N2, Canada
John B Seal, Markus Selzner, Department of Surgery, University of Toronto, Multiorgan Transplant Program, Toronto General Hospital, ON M5G 2N2, Canada
Author contributions: Bazerbachi F and Selzner M designed the research and wrote the paper; Seal JB and Selzner M designed the research, wrote the paper and revised the paper.
Correspondence to: Markus Selzner, MD, Assistant Professor of Surgery, Department of Surgery, University of Toronto, Multiorgan Transplant Program, Toronto General Hospital, NCSB 11C-1244 585 University Avenue Toronto, ON M5G 2N2, Canada. markus.selzner@uhn.ca
Telephone: +1-416- 3405230 Fax: +1-416-3405242
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Abstract

The scarcity of donor livers has increased the interest in donation after cardiac death (DCD) as an additional pool to expand the availability of organs. However, the initial results of liver transplantation with DCD grafts have been suboptimal due to an increased rate of complications, as well as decreased graft survival. These challenges have led to many developments in DCD donation outcome, as well as basic and translational research. In this article we review the unique characteristics of DCD donors, nuances of DCD organ procurement, the effect of prolonged warm and cold ischemia times, and discuss major studies that compared DCD to donation after brain death liver transplantation, in terms of outcomes and complications. We also review the different methods of donor treatment that has been applied to ameliorate DCD organ outcome, and we discuss the role of machine perfusion techniques in organ reconditioning. We discuss the two major perfusion models, namely, hypothermic machine perfusion and normothermic machine perfusion; we compare both methods, and delineate their major differences.

Key words: Transplant hepatology; Liver transplantation; Organ donation; Extended criteria donors; Donation after cardiac death; *Ex-vivo* liver perfusion; Normothermic machine perfusion; Hypothermic machine perfusion

Core tip: There exists an increased need for liver grafts that currently exceed the availability of organs by a large margin. It is estimated that a third of the patients awaiting for transplantation will perish or become too ill due to the scarcity of grafts. This has led to a renewed interest in marginal organs as a potential pool. Most notably, donation after cardiac death livers has been targeted, and new strategies emerge to ameliorate their quality. *Ex-vivo* liver perfusion techniques could drastically change the paradigm of organ preservation, conditioning, and amelioration.

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INTRODUCTION

Donation after cardiac death (DCD) was the only mode of organ retrieval in the beginning of organ transplantation era. It was largely abandoned after the establishment of brain death criteria in favour of heart beating organ retrieval to minimize ischemic injury. However, the increasing organ shortage has resulted in a new interest to

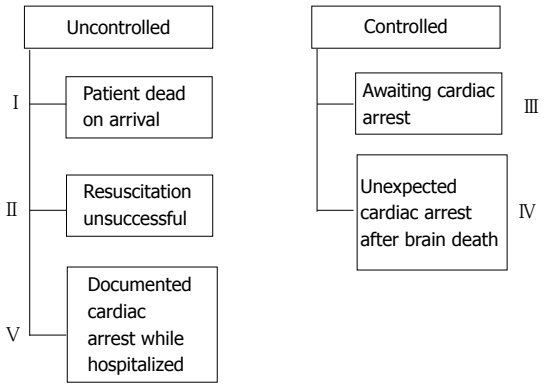

Figure 1 The maastricht classification of donation after cardiac death donors.

extend the donor pool for liver transplantation. Excellent outcomes have been reported for kidney transplantation with DCD organs, which triggered new interest for DCD liver transplantation in the 90's. One study concluded that DCD liver grafts can be used to dramatically reduce wait list time with outcomes comparable to those of standard criteria and donation after brain death (DBD)[1]. Another study reported that a 5% increase in DCD donors will lead to a 27% relative reduction in the wait list volume[2]. The proportion of DCD organs has increased compared with the past decades, and DCD liver transplantation remains at approximately 6% in the United States[3]. However, this group of marginal organs is characterized by increased sensitivity to preservation injury, and the ischemia-reperfusion injury (IRI) pathway is exacerbated by the combination of warm and cold ischemia resulting in cellular injury and energy depletion.

CHARACTERISTICS OF DCD DONORS

In contrast to the irreversible coma state that defines brain death[4], cardiac death is the irreversible desist of respiratory and circulatory functions. DCD donors [also known as non-heart-beating donors (NHBD)] are divided according to the modified Maastricht classification into 5 categories, which can further be reduced to two main groups (Figure 1): (1) Controlled DCD (categories Ⅲ and Ⅳ), wherein circulatory and respiratory organ support is voluntarily withdrawn by the medical provider, in the setting of a dismal prognosis that renders cardio-respiratory support no longer in the patient's best interest and survival is deemed futile; and (2) Uncontrolled DCD (categories Ⅰ, Ⅱ, and Ⅴ), in which cardiac death occurs suddenly, and resuscitation is unsuccessful or absent[5].

Debate is ongoing regarding the exact definition of cardiac death, and whether loss of cardiac electricity should be established *vs* solely relying on the absence of heart sounds, pulse, and blood pressure[5-7]. Today, the irreversible absence of pulse is accepted as the moment of death.

DCD ORGAN PROCUREMENT

After death is announced, organ procurement starts following a mandatory interlude designated to monitor for spontaneous return of cardiopulmonary function. The American Society of Transplant Surgeons (ASTS) recommends 2 min wait time, and the Society of Critical Care Medicine (SCCM) and Institute of Medicine (IOM) recommend 5 min of sustained death prior to the commencement of procurement[8,9] (Figure 2).

The first described technique for DCD graft retrieval was the so-called "super-rapid technique" (SRT) presented by Starzl *et al*[10], and involved en-bloc resection of the abdominal viscera, with subsequent separation of individual organs on the back-table while immersed in ice[10,11]. This technique has been further refined, and the modified technique entails a fast thoraco-laparotomy, hypothermic perfusion of the abdominal aorta, venous exsanguination, cross-clamping of the supradiaphragmatic aorta, and may include portal venous hypothermic perfusion[8]. The rate-limiting step in terminating warm ischemia time (WIT) is the cannulation of the aorta to allow hypothermic perfusion. In experienced centers, this essential step could be done within 1-2 min after declaration of death[12].

In-situ cooling of the liver before and during procurement is imperative. Some have advocated for precannulation of the femoral arteries prior to withdrawing life support to further shorten the time until initiation of the cold flush. A double-balloon, triple-lumen (DBTL) catheter can be used to shunt the cold perfusate solely to abdominal viscera[13]. Although cooling of abdominal organs is facilitated with this technique, ethical concerns have impeded its utilization[14-16].

The role of the initial flushing solution has been controversially debated. DCD rat livers that were flushed with low viscosity solutions showed lower vascular resistance than those flushed with cold Belzer solution [University of Wisconsin solution (UW)] and led to better survival[17]. In contrast, analysis of the UNOS database showed a decrease in graft survival when Histidine–Tryptophan-Ketoglutarate (HTK) *vs* UW solution was used as a preservative solution in DCD organs[18].

THE CONCEPT OF WARM ISCHEMIA TIME

Warm ischemia time (WIT) refers to cellular ischemia under normothermic conditions, and entails two physiological periods[19,20]: (1) Ischemia after withdrawal of life support until cold perfusion is commenced; and (2) Ischemia during implantation, after removal of the organ from ice until reperfusion.

The beginning of asystole is difficult to predict following the withdrawal of life support therapies (WLST). Should asystole not happen within 120 min of WLST, current guidelines recommend ending the attempted DCD organ retrieval and continuing ICU therapy. In about 30% of all attempted DCD organ retrievals death does not occur within the 120 min recommended waiting time. Different time points from the beginning of warm ischemia have been used. Some groups propose the use of total WIT

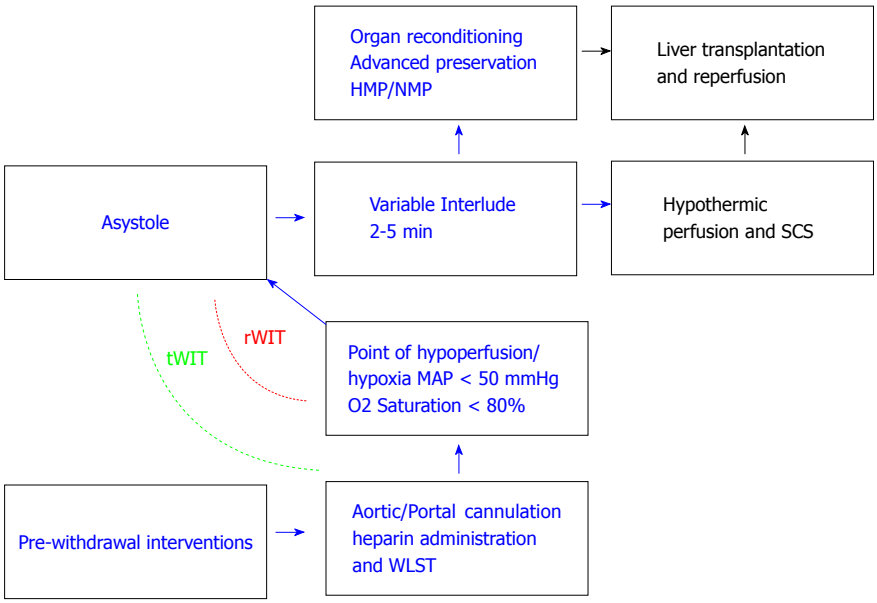

Figure 2 Donation after cardiac death organ procurement algorithm. Modified from Abradelo De Usera *et al*[24]. HMP: Hypothermic machine perfusion; NMP: Normothermic perfusion; SCS: Static cold storage; WLST: Withdrawal of life support therapies.

(tWIT): entailing the period from WLST until the start of preservation (whether it is sought through static cold storage (SCS), or through extracorporeal perfusion, organ preservation starts either as a total body cooling approach, or as in-situ cooling approach using the DBTL catheter[21-24]). In contrast, others have proposed to consider the beginning of warm ischemia only if the arterial saturation of oxygen falls under 70%-80% and/or arterial hypotension occurs (MAP < 60-50 mmHg), also dubbed real warm ischemia time (rWIT). It ends once preservation commences[24,25]. According to the ASTS, the maximal acceptable WIT for safe liver transplant is 30 min or less[8,26].

Interestingly, single center studies produced conflicting reports regarding the association between WIT and graft survival[27-29]. Similarly, the association between WIT and the rate of biliary complications has not been consistently established in all available studies[28,30-32]. However, despite the inability to detect these associations, Ho *et al*[29] have shown that longer rWIT may predict poor survival after liver transplantation. Another recent study by Abt *et al*[33] demonstrated in a multivariate regression analysis, an association between graft survival and the slope of the systolic blood pressure using values during the first 10 min after donor extubation (SBP10). The authors propose to select donors with a favorable trajectory of blood pressure during the agonal phase[33].

Warm ischemia injury is mediated by several mechanisms, including Na^+/K^+-ATPase dysfunction, inhibition of nitric oxide synthase (NOS), vascular microthrombosis, changes in bile salts composition, overproduction of hypoxanthine and free radicals, as well as overproduction of vasoconstrictors during reperfusion[34-39].

LIVER TRANSPLANTATION WITH DCD GRAFTS: OUTCOMES AND COMPLICATIONS

Reich *et al*[40] reported the first single-center experience with comparable outcome of DCD *vs* DBD liver transplantation. However, major studies that followed reported conflicting results (Table 1).

The initial outcomes of liver transplantation with DCD grafts have been suboptimal due to a high rate (20%-40%) of ischemic-type biliary strictures (ITBS)[36,41-43], higher graft failure rate, as well as increased medical and surgical complications following the procedure.

According to one study by Jay *et al*[44], post transplantation costs were significantly higher in DCD versus DBD transplant recipients who experienced ITBS or re-transplantation. In their study, DCD costs continued to be higher when the analysis was censored for re-transplanted patients; this may suggest that morbidity is increased and may account for this increase in costs[44]. It follows that an examination of the most common complications of DCD liver transplants may be necessary, if the full scope of economic burden is to be understood[45].

Interestingly, in a study comparing 24 DCD recipients *vs* 16 DBD recipients, Yamamoto *et al*[45] showed that, despite an increased rate of hepatic artery thrombosis (HAT) and biliary complications, graft and patient survival did not differ between the groups. Their study suggested that improved surgical and medical management has led to amelioration of transplantation outcomes.

One of the immediate complications is primary graft failure (PGF) following ischemic insult resulting in re-transplantation or patient death. PGF after DCD liver transplantation has decreased in frequency over time, and is reported to be approximately 5% in the most recent studies[31,43,46]. This improvement may be ascribed to improved surgical techniques and amelioration in organ preservation and extraction.

One of the later complications is ITBS [also dubbed as nonanastomotic biliary stricture (NABS), or ischemic cholangiopathy]. ITBS presents as non-anastomotic intrahepatic or extrahepatic biliary strictures (in the absence of arterial thrombosis), which occur within the first 3 mo

Table 1 Major studies that compared donation after cardiac death vs donation after brain death liver transplantation outcomes

Ref.	Year	DCD transplants number	Recipient survival rate (%) at 1 yr, 3 yr, and 5 yr post-transplant			Graft survival rate (%) at 1 yr, 3 yr, and 5 yr post-transplant			ITBS rate	Retransplants rate
Croome *et al*[98]	2013	HCC DCD = 242				76	64	56		
		Non-HCC DCD = 2117				86	77	71		
Abt *et al*[33]	2013	110						47		14%
Callaghan *et al*[99]	2013	352		81			73			
Vanatta *et al*[100]	2013	38	92	80		92	74		7%	2%
Elaffandi *et al*[101]	2012	108	84							2%
Taner *et al*[28]	2012	200	93	85	81	81	73	69	12%	5%
Meurisse *et al*[52]	2012	30	93	85	85	90	82	82		3%
DeOliveira *et al*[30]	2011	167	87	85	81	85	83	78	2%	
Hong *et al*[102]	2011	81				78	62	53	10%	12%
Mathur *et al*[53]	2011	1567					65			13%
Dubbled *et al*[46]	2010	55	85	80		74	68		14%	18%
Yamamoto *et al*[45]	2010	24	62	43	43	54	37	38		
Detry *et al*[103]	2010	58	83	67		72	49		38%	
de Vera *et al*[27]	2009	141	79		70	69		56	16%	18%
Grewal *et al*[43]	2009	108	92	88	88	79	74	71	8%	15%
Jiménez-Galanes *et al*[104]	2009	20	86			80			5%	
Pine *et al*[105]	2009	39	82	68		80	64		20%	
Nguyen *et al*[42]	2009	19	90		90	74		63	10%	16%
Fujita *et al*[106]	2007	24	87	82		69	56			21%

DCD: Donation after cardiac death.

after transplantation. One hypothesis of ITBS etiology is the arterial supply theory. Since most of the blood that supplies the biliary system emanates from the hepatic arteries, severe decrease in hepatic artery supply may result in biliary necrosis and subsequent stenosis[47,48]. The occurrence of this complication has been estimated to fall between 20% and 40% in DCD recipients, compared to 5% in DBD recipients However, recent studies reported a decreased frequency of this complication, and estimated its incidence to be around 10%[30,31,49].

ITBS appears to be particularly associated with DCD organs, with a 10 fold increase in incidence compared with DBD livers. Other risk factors are increased donor age, increased donor weight, and increased cold ischemia time (CIT) and/or WIT (especially WIT > 30 min)[27,28,32,50-54].

Attempts have been made to reduce ITBS in orthotopic liver transplantation. Moench *et al*[55] established the utility of arterial back-table pressure perfusion of the hepatic artery prior to transplantation in heart beating donor grafts, and showed an association with decreased ITBS rate in a multivariate analysis. Hashimoto *et al*[36] investigated the use of tissue plasminogen activator (tPA) administration in 22 patients during DCD liver transplantation. In the implantation phase, tPA was injected in the hepatic artery prior to making the anastomosis. The authors found that this strategy decreased the incidence of ITBS to 9% in DCD liver grafts[36].

WHO SHOULD RECEIVE DCD LIVERS?

As a result of these complications, strict acceptance criteria have been applied for DCD liver transplantation and only a small percentage of DCD livers are currently accepted for transplantation. Harring *et al*[56] proposed criteria for DCD transplant optimization that focused on strict selection for donors and recipients (donor age < 50 years and WIT < 20 min), however, current ASTS recommendations state that DCD liver grafts should be ideally used in younger recipients with age < 60 years and WIT < 30 min.

Some studies cautioned about using DCD grafts in HCV(+) recipients as they have found that HCV recurrence was more aggressive and advanced more rapidly in this cohort of patients, compared to DBD grafts[57,58], although a recent registry analysis failed to detect this difference[59]. Moreover, a recent match-controlled, retrospective analysis demonstrated that DCD liver grafts did not promote disease progression or negatively affect patient and graft survival in comparison with DBD liver grafts in HCV(+) patients[60].

DONOR TREATMENT

Animal models were designed using several strategies to optimize DCD grafts, including administration of different pharmacologic agents[61,62]. Administration of heparin and phentolamine prior to asystole resulted in an increase of acinar perfusion and sinusoidal density in rat livers[61]. Experimental data have shown that tacrolimus may incur protection against hepatic IRI when administered intravenously or as a hepatic rinse[63]. Recently, a study protocol has been published for a European randomized multicenter trial comparing *ex vivo* tacrolimus perfusion of marginal liver grafts *vs* placebo[64]. Milrinone, a phosphodiesterase 3 inhibitor, exerts positive inotropic and vasodilatory effects, and has been reported to attenuate the graft injury caused by CIT, WIT, and subsequent IRI *via* an increase in intracellular cAMP levels[65]. Pentoxifyl-

line is a methylxanthine compound and a phosphodiesterase inhibitor with hemorheological, as well as anti-inflammatory properties has also been shown to decrease IRI in animal models[66,67].

MACHINE PERFUSION TECHNIQUES

As more programmes now accept increasing numbers of DCD livers in which organ function status is uncertain, the need for further evaluation and even reconditioning of the organ is emphasized.

Although the prevailing goal of organ preservation in the past has been to slow the metabolic rate by SCS, this strategy may not be optimal for livers from marginal donors.

Initially, SCS emerged as a method to optimally store organs and thus improve graft survival. However, this simple technique does not allow for adequate evaluation of the organ, as reduction of metabolism to about 5% by cold storage hinders the possibility of meaningful liver evaluation. Moreover, while hypothermia slows down metabolism, it does not prevent continuation of anaerobic glycolysis and does not stop the production of harmful by-products.

Therefore, several groups proposed the use of extracorporeal perfusion systems to reduce IRI, and ameliorate graft outcomes.

Originally suggested by Carrel and Lindbergh in the late 1930s for organs in general, *ex vivo* liver perfusion emerged as a potential protective strategy[68-72]. The purpose of extracorporeal perfusion is to continuously support the preserved organ with nutrients and oxygen, and to eliminate toxic products from the cellular milieu. Newer studies evaluated these experimental techniques and their effect on late biliary injury[73].

Ex vivo perfusion systems could be classified according to the perfusate temperature, and it includes: normothermia (35 ℃-37 ℃), mild hypothermia/subnormothermia (32 ℃-35 ℃), moderate hypothermia (28 ℃-32 ℃), severe hypothermia (20 ℃-28 ℃), and profound hypothermia (< 20 ℃)[74] (Table 2).

Henry *et al*[75] and Guarrera *et al*[76-78] performed hypothermic (4 ℃) machine perfusion (HMP) of the hepatic artery and portal vein without oxygenation. The authors used sub-physiologic perfusion pressures, and no benefits of hypoxic HMP were observed in an animal model. However, in a case control study with 20 human liver transplants using low risk donors, the same group observed a decrease of serum AST/ALT after transplantation when HMP was compared with SCS.

In another porcine DCD model, de Rougemont *et al*[71] studied the effects of oxygenated HMP prior to transplantation. Livers were exposed to 1 h WIT followed by 7 h of SCS preservation or 1 h of WIT plus 6 h of SCS and 1 h of oxygenated HMP. After liver transplantation, AST levels were similar in both groups. Median recipient survival after transplant was slightly increased by oxygenated HMP from 5 to 8 h.

Despite these results, early experiments that examined machine perfusion of animal liver grafts showed that a hypothermic perfusate is a risk factor for post-transplant HAT. Ikeda and colleagues demonstrated that, compared to normothermic perfusion (NMP), HMP was associated with increased hepatic artery resistance and decreased bile flow[79]. More recently, Tolboom *et al*[80] showed that bile production increased concordantly with increased perfusate temperature, and was the highest at a degree of 37 ℃[80]. Consequently, there existed an increased interest in normothermic techniques[81].

In 2001, Schön *et al*[82] were the first to successfully describe NMP in porcine livers. The Oxford group headed by Dr. Peter Friend showed conserved hepatic function with NMP up to 72 h[83-85]. SCS cannot be completely avoided, even in NMP, due to the complexity of the procurement process, as well as the logistics of the apparatus. Although NMP could not salvage porcine livers that received 4 h of SCS prior to perfusion, it was able to assess liver function, and maintain cellular replenishment when used throughout the preservation period[83,85-87]. Brockmann and colleagues showed that NMP was advantageous to DBD and DCD livers that endured a prolonged period of preservation (approximately 20 h)[72].

Our group in Toronto[70] was the first to examine bile duct injury using NMP in a DCD porcine model while simulating transplantation. Our study was designed to simulate a clinical scenario in which organs are retrieved at a remote donor hospital and transported with SCS to the transplant center to commence NMP, and our machine perfusion model utilized Steen solution[88] for preservation rather than cellular products. Livers managed with SCS alone had significantly higher ALT levels, decreased oxygen extraction, and increased hepatic necrosis. Levels of bilirubin, phospholipids and bile salts in the bile fluid were fivefold decreased, while LDH was sixfold higher in the SCS *vs* NMP group. Hepatic artery perfusion was decreased and bile duct necrosis was increased as well, favoring NMP. The protective mechanisms of machine perfusion remain under investigation[89].

Despite these advances, the majority of the studies that examined machine perfusion, focused on early liver graft injury and acute survival. However, in humans, the majority of biliary lesions occur within the first year after transplantation[90].

OUTLOOK FOR FUTURE RESEARCH

Regional perfusion (RP) of the liver is used in-vivo, prior to organ retrieval, and act as a bridge between asystole and retrieval, thus limiting WIT, and mitigating ischemia. Moreover, it prevents the depletion of mitochonodrial ATP stores, favoring aerobic metabolism, and acting as an ischemia pre-conditioning period[91-93].

Future research is needed to focus on synergistic liver perfusion modalities such as RP extracorporeal oxygenation, followed by NMP.

The NMP system could also benefit from optimiza-

Table 2 Hypothermic *vs* normothermic machine perfusion of liver grafts

Hypothermic machine perfusion HMP	Normothermic machine perfusion NMP
Temperature 0 ℃-4 ℃	Temperature 37 ℃
Logistically easier	Logistically demanding
Modest resumption of energy production with low perfusion rate	
Improves the state of mitochondria during preservation	Recreates the physiological milieu by maintenance of normal temperature
Performed at sub-physiologic pressures[107]	Performed at physiological pressures[70,82]
Requires low perfusion rates[108]	Requires high perfusion rates[108]
No requirement for a specific oxygen carrier in the perfusate as demand for O_2 is low[108]	Oxygen is provided by using blood, modified hemoglobin, or using a high oxygen tension in special preservation solutions[70,82,84,88,109]
Less occurrence of graft infection considering the hypothermic state	Reduces IRI
More tendency for endothelial cell, kupffer cell, and macrophage cell damage due to shear stress and hypothermic activation[110-113]	
When compared to SCS it decreases inflammatory cytokines but no difference in graft or patient survival was found[77,114]	Provides nutrients (glucose, amino acids, *etc.*), medications to prevent micro-circulatory failure (*e.g.*, prostacyclin, heparin, antibiotics), and oxygen
May help protect marginal livers by converting PNF into allograft dysfunction[71]	Allows the assessment of organ viability (*e.g.*, Galactose elimination, factor V production, bile flow)
	May allow the use of gene therapy prior to transplantation, to reduce the risk of rejection, or decrease the ischemia-reperfusion injury[115-117]

HMP: Hypothermic machine perfusion; SCS: Static cold storage; NMP: Normothermic perfusion.

tion in terms of portability. In its current form, NMP-dependent techniques cannot avoid a period of SCS prior to perfusion. Experimental data suggest that prolonged cold ischemia of the organ before attachment to the *ex-vivo* perfusion system could impair the protective effects[86,94].

Another area to explore is liver assessment methods during *ex-vivo* perfusion to predict function and viability of DCD liver grafts. If clinical validation of such parameters could be established, the procurement team would be able to determine suboptimal grafts without putting the recipient at risk with the liver transplant procedure. Alternatively, optimal DCD grafts would avoid unjustified rejection, therefore adding more livers to the donor pool[87].

NMP may also provide ground for pre-transplantation gene therapy of donor grafts. Cypel *et al*[95] investigated this method with an adenoviral vector encoding human interleukin-10 (AdhIL-10) to repair injured donor lungs *ex-vivo* (through NMP) before transplantation. In their study, AdhIL-10-treated lungs showed significant improvement in function when compared to controls, a favorable shift from proinflammatory to anti-inflammatory cytokine expression, and recovery of alveolar-blood barrier integrity[95]. The range of potential targets for gene therapy prior to transplantation includes recruitment of heat shock proteins (some of which have been shown to protect against IRI[96]), modulation of co-stimulatory and apoptosis pathways, amelioration of immunologic profile to prevent rejection, and manipulation of leukocyte recruitment[87,97].

CONCLUSION

The scarcity of donor livers has resulted in an increased interest in extended criteria donors (ECD), and more specifically DCD grafts, as a potential source to significantly expand the donor pool. Initially, this pool provided disappointing results as it was associated with high incidence of ITBS, HAT, and PGF, however, outcome has improved with better donor selection and pre-transplant treatment. Future application of machine perfusion modalities might allow graft assessment and repair, resulting in more extensive use of DCD liver grafts and provide ground for pre-transplantation conditioning of organs.

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