The benefits & challenges of DCD liver transplantation: review of the literature

THE INTRODUCTION OF DCD GRAFTS

DCD (or at that time so-called non-heart beating donation) has been explored since the start of human organ transplantation. In fact, the first human heart, lung, kidney and liver transplants were performed with DCD grafts (1–4). However, since the Harvard consensus report to determine brain death in 1968, liver transplantation with organs retrieved from brain death donor became the golden standard (5). Due to the rapid developing organ shortage, donation after circulatory death was revived in the Western world during the early 1980s, with a pioneering role for the Netherlands using DCD kidneys for transplantation (6). Due to the complexity of the surgical procedure, the immediate life-saving concept and potential lethal complications, it took a bit more time for transplant surgeons to engage in DCD liver transplantation, but DCD grafts are part of the liver transplantation practice since the early 2000s in North America and many European countries.

Classification of DCD donation

Starzl and colleagues reported in 1995 their first series of thirteen DCD grafts used for transplantation (7). They used two types of grafts:

§ Uncontrolled DCD grafts: a patient that is (in the process of being) pronounced brain death, with a sudden, unexpected cardiac arrest. Thereafter, cardiopulmonary resuscitation CPR is started and the patient is transported to theatre for the organ donation procedure.

§ Controlled DCD grafts: a patient has irreversible neurological damage, but either do not fulfil the brain death criteria or the family requests withdrawal of life support before organ donation. In these cases, the life support is withdrawn and the organ procurement procedure starts after a certain period (variable between countries) after circulatory arrest.

As expected, the actual transplantation rate of livers from potential donors was higher in the controlled group (86% vs. 60%). The results of the uncontrolled DCD grafts were disappointing, with half of the patients requiring immediate retransplantation due to PNF and inadequate portal flow and two other patients lost their grafts later due to other causes. All the grafts after controlled DCD donation functioned well (n=6) and after two years three patients were alive with functioning grafts. In the following years, the option of DCD grafts was explored in other countries. The widely used 'Maastricht Classification' (**Table 1**) for DCD donation were introduced by Kootstra and colleagues in 1995, stratifying the potential DCD donors into four (and later five) groups (8–10). This classification is more specific about the location and unexpected

Table 1 – Modified Maastricht classification for donors after circulatory death
Adapted from Thuong *et al*, Transplant International, 2016 (10).

Category I	*Found dead out of hospital*
Uncontrolled	IA. Cardiocirculatory death outside hospital with no witness. Totally uncontrolled.
	IB. Cardiocirculatory death outside hospital with rapid resuscitation attempt.
Category II	*Unsuccessful resuscitation*
Uncontrolled	IIA. Unexpected cardiocirculatory death in ICU
	IIB. Unexpected cardiocirculatory death in hospital with rapid resuscitation
Category III	*Awaiting cardiac arrest*
Controlled	IIIA. Expected cardiocirculatory death in ICU
	IIIB. Expected cardiocirculatory death in OR (withdrawal phase >30 min)
	IIIC. Expected cardiocirculatory death in OR (withdrawal phase <30 min)
Category IV	*Cardiac arrest while brain death*
Uncontrolled	IVA. Unexpected cardiocirculatory arrest in a brain dead donor (in ICU)
Controlled	IVB. Expected cardiocirculatory arrest in a brain dead donor (in OR or ICU)
Category V	Euthanasia
Controlled	VA. Medically assisted cardiocirculatory death in ICU or ward.
Uncontrolled	VB. Medically assisted cardiocirculatory death in OR.

aspect of the DCD donation. The most common used categories are II (uncontrolled) and III (controlled). Liver transplantation with type II DCD donors has been common practice Spain and has later been explored in Italy and France (11–13). Due to the unpredictable warm ischemia times in type II DCD liver grafts, the outcomes of liver transplantation with these grafts are capricious with higher rates of PNF and biliary complications, with initial one-year graft survival rates of only 50% (14,15). The Spanish law allows for premortal cannulation of the donors and therefore, the clinicians quickly engaged in the use of perfusion techniques with cardiopulmonary bypass of the donor, to limit the warm ischemia times and to optimize organ quality. Although initially only a small percentage of the potential grafts were used for transplantation, the results of this normothermic regional perfusion with type II grafts were improving and therefore it is now common practice in this country (16,17).

Type III DCD organ donation

All the following chapters in this thesis will concern liver transplantation with *type III controlled DCD grafts*. Type III DCD organs have been the preferred option from the beginning in the US, Canada, and several European countries, including the Netherlands, Belgium and the UK (18). Regularly, a type III DCD donor is admitted on ICU and there is a controlled WoT. This can either be either in ICU, anaesthetic room or

operation theatre. After circulatory arrest, there is an obligatory waiting time before death can be declared. This time is 5 minutes by law in the Netherlands, but varies between 5 and 20 minutes in Europe (10). Because the general practice for WoT in the Netherlands is on ICU, there is an additional transport time of the donor to the operation theatre, which extends the period of donor warm ischemia time (DWIT) (19). The aim of the organ procurement in DCD donation is to safely retrieve the organs as quickly as possible. The principle of the super-rapid technique consists of coordinated surgical steps including a rapid thoraco-laparotomy, cannulation of the abdominal aorta for cold perfusion, venous exsanguination and cross-clamping of the thoracic aorta and followed by separate resection of all organs (20). An overview of organ donation by graft type in the Netherlands during the last years is displayed in **Figure 1**, showing a steady increase of controlled DCD donation from the year 2000 (21). After the start of the DCD program in 1999, due to a part of the donors that do not proceed to donation and a number of liver grafts discarded before implantation, the number of liver transplants performed with DCD grafts grew at a slower pace (**Figure 2**), with 45 DCD transplants in 2014.

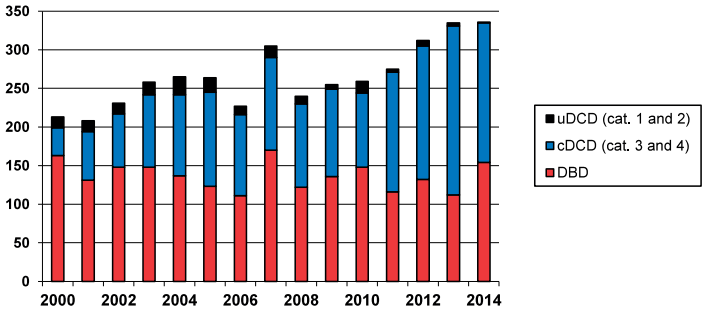

Figure 1 – Number of deceased organ donors in the Netherlands
From Leiden *et al*, Netherlands Journal of Medicine, 2016 (21).

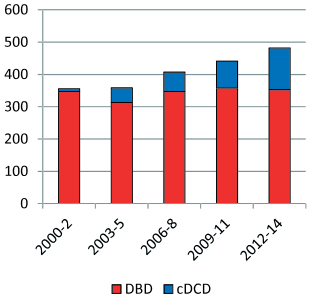

Figure 2 – Liver transplantation by graft type in the Netherlands since 2000
From Leiden et al, Netherlands Journal of Medicine, 2016 (21).

Donor warm ischemia time

The obligatory DWIT in DCD donation is responsible for the additional period of warm ischemia and aggravation of hepatic IRI (22). **Figure 3** shows an overview of the separate period between the WoT until the start of cold perfusion. At this moment, there is no consensus about the actual definition of DWIT and various definitions are used (10). Overall, DWIT can be divided into two periods: the agonal phase (from WoT until circulatory arrest) and the asystolic phase (from circulatory arrest until the start of cold perfusion). For the graft to be considered for liver transplantation, the length of the full period of DWIT cannot extend one hour in most countries, including the UK and the Netherlands (23,24). On average, the time for a potential DCD donor to die is 36 minutes (25). However, DWIT is a dynamic period and some donors have a much longer period of hypoxia or hypotension during the agonal phase, with a potential major impact on the severity of hepatic IRI. The impact of DWIT on postoperative outcomes after DCD liver transplantation has been studied before, but different definitions of DWIT were used and consequently, the length of an acceptable DWIT in these studies ranges from 10 to 35 minutes (26–30). A common way to assess DWIT is with the functional DWIT. This period is a combination of agonal phase starting with the drop in saturation (SpO2 <80%) or blood pressure (MAP or SBP <50 mm Hg), until the start of cold perfusion. In many countries, the cut-off for discarding a DCD liver is 30 minutes of functional DWIT.

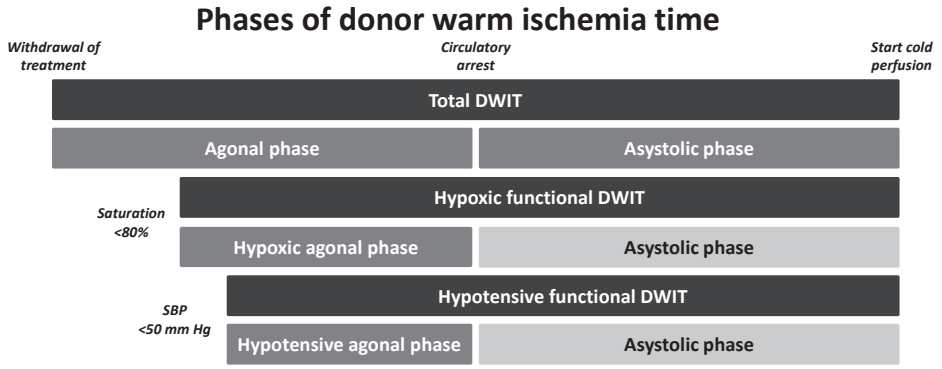

Figure 3 – Overview of the separate periods of donor warm ischemia time

The potential of expanding the donor pool

Even after more than 20 years of liver transplantation with DCD grafts, there are no exact numbers on what the real contribution of DCD grafts is to the patients waiting for a liver. Transplantation with DCD grafts comes with a certain risk of PNF or other complications and some patients will even die before a second organ becomes avail-

able. Therefore, the actual benefit and perspective for the patient on the waiting list is more complicated to estimate. In an early nationwide comparative study from US (2006) of DCD and DBD grafts, an increased relative risk (RR 1.85) for graft failure was reported with the use of DCD grafts (31). However, a following study in 2014 with US *United Network for Organ Sharing* (UNOS) data confirmed the inferior graft survival rates with DCD grafts, but the patient survival on the long-term was comparable with DBD grafts, implicating these patients are relisted an retransplanted timely (32).

Survival outcomes in comparison with DBD grafts

Since the start of DCD liver transplantation, multiple groups from all over the world have reported their experience with these grafts, some of them also comparing the results with DBD grafts. The first report from the University of Wisconsin with 19 DCD grafts in 1999, already reported an increased incidence of PNF leading to more graft loss in this group, but comparable patient survival with recipients of DBD grafts (33). In the following years, more centres reported their experience with mixed results (34,35). National data from US arrived in 2003, summarizing the centre experiences, with increased retransplantation rates and inferior survival with the use of DCD grafts (36). The first results from Europe (King's College, UK) were promising, with satisfactory results with grafts of selected DCD donors (37). Results of the Dutch DCD program (2010) were similar, with satisfactory survival rates, despite a higher risk for biliary strictures (38). Importantly, duration of DWIT and cold ischemia time were both identified as risk factors in DCD liver transplantation and should be minimized. Additional donor risk factors for DCD graft failure that are identified are older donors and high donor weight (graft steatosis). Older recipients, those with high MELD-scores (>35) and life-support prior to transplantation are also at increased risk for graft failure (28).

With the additional risk of DCD grafts in mind, many have adapted the strategy to allocate these grafts to recipients with lower MELD-scores, such as patients with HCC at risk for exceeding Milan-criteria (39,40). This leads to differences between DCD and DBD liver transplantation in donor, graft and recipient risk factors, compromising the analysis of outcome. Therefore, several groups have published their data using propensity score matching, a method to equalize study groups in non-randomised studies, by matching the cases of the intervention group (DCD) to certain cases from the control group (DBD) by preselected characteristics (41). The studies from the early years in DCD liver transplantation and those performed without matching demonstrate mixed positive and negative results. Interestingly, the general sentiment of the five studies using propensity score matching display significant inferior results

with DCD grafts: PNF and ITBL were more frequently observed in recipients of DCD grafts that were matched to a DBD counterpart, leading to inferior graft and overall survival rates (30,42–45). The overall negative results of these studies with matched cases shows the 'real' additional risk of DCD donation in comparison to brain-death donors. It also suggest that balancing the risk between donor and recipient in a combined DCD & DBD donor pool is essential to optimize the results of the population on the liver transplant waiting list.

The trends from studies published in the last three years is that the known complications of using DCD grafts are still a serious issue and these patients have an increased risk for graft loss (29,44). However, due to the early identification of patients with serious complications, they can be relisted earlier and receive optimal bridging treatment towards retransplantation, leading to comparable patient survival on the long-term (29). The Birmingham group from the UK has used more marginal DCD grafts over the last years, with comparable survival rates with DBD grafts, by selecting the right patient to receive a DCD graft (44). More recently, they have shown that DCD grafts from older donors are not associated with poorer outcomes, provided that other risk factors are eliminated (46). Historically, transplant surgeons in the US have been more cautious with the use of DCD grafts, displayed by the low rate of DCD liver transplantation nationally (only 6% of total deceased donor transplants in 2016 (47). However, recently voices arise in the US to approach DCD grafts with a different strategy to limit the duration of cold ischemia time and only select patients with relatively low MELD-scores (48).

Specific postoperative complications

Primary non-function

Due to the additional warm ischemic period during DCD donation, there is a significant depletion of intracellular energy reserves leading to more severe hepatic IRI (49). Prolonged duration of DWIT has been linked to non-viability of DCD grafts in pigs and the first studies in humans already showed higher incidence of PNF (7,33,36,50). Incidence rates up to 12% of have been reported over the years, but this was not always significantly more compared to DBD grafts (30,35,36,51,52). Furthermore, some have described their DCD experience without any cases of PNF (53–55). Additional to a long DWIT, donor age, graft steatosis and prolonged cold ischemia are thought to increase the risk for PNF (56).

Ischemic-type biliary lesions

Biliary complications are considered the Achilles heel of DCD liver transplantation. Especially strictures not related to the biliary anastomosis created during the transplant, the so-called non-anastomotic strictures, ischemic cholangiopathy or ischemic-type biliary lesions (ITBL) are more frequently observed when DCD grafts are used. ITBL are defined as symptomatic strictures of the intrahepatic or hilar bile ducts after liver transplantation, in the presence of a patent hepatic artery (57). Every graft prepared for liver transplantation experiences a certain period of warm and cold preservation, leading to significant injury to the luminal biliary epithelium, but this does not necessarily lead to ITBL. Although the exact pathogenesis of ITBL remains unknown, recent literature proposes that injury to specific components of the bile duct, i.e. the peribiliary glands and vascular plexus during preservation is associated with develop-

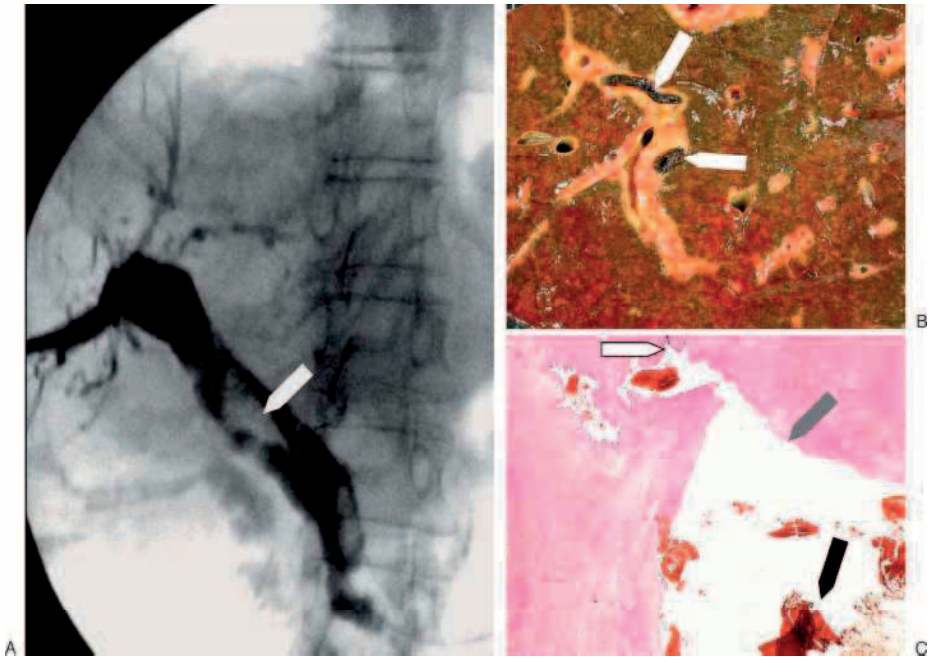

Figure 4 – Macroscopic, radiological and histological appearance of ITBL after liver transplantation.
From Deltenre *et al*, Seminars in liver disease, 2008 (62).
Biliary casts. (A) Typical appearance on endoscopic retrograde cholangiopancreatography in a patient with ischemic cholangiopathy following liver transplantation. Filling defects (white arrow) can be seen in dilated bile ducts, with mildly irregular margins. (B) Gross appearance at sectioning in an excised liver. Solid brown material can be seen within large bile ducts (white arrows). (C) Microscopic appearance of a large bile duct. Biliary epithelium is lacking in some areas (gray arrow) and is reserved in other areas (white arrow). Solid, bile-stained material is observed within the lumen (black arrow). (Courtesy of Dr. Annie Sibert, Service de Radiologie, and Dr. Vale´ rie Paradis, Service d'Anatomie et de Cytologie pathologiques, Hôpital Beaujon, Clichy, France.)

ment of ITBL (58,59). This suggests that adequate preservation of these structures is essential for a timely regeneration of the biliary epithelium. Additional damage of bile salts after transplantation and subsequent influx of immune cells leading to inflammation and fibrosis can result in ITBL (60). The extra period of warm ischemia during DWIT potentially leads to the additional injury of the vital structures of the biliary tree, increasing the risk for development of ITBL with DCD grafts. Patients can develop the strictures within months after liver transplantation (**Figure 4**), regularly requiring endoscopic and surgical interventions, but often retransplantation cannot be avoided (61).

In the largest meta-analysis (2011) about ITBL after DCD liver transplantation comprehending 11 studies by Jay et al, ITBL was observed in 16% of the recipients receiving a DCD graft and they had an 10.8x increased odds of developing ITBL, compared to DBD recipients (63). As a result, DCD recipients also had a 2.6-fold increased odds of retransplantation. A more recent meta-analysis from 2014 showed similar results with ITBL occurring in 16% and 3% after liver transplantation with DCD and DBD grafts, respectively (64). ITBL has a multifactorial origin and a wide variety of ITBL-rates have been observed between single-centre experiences and ranges from 3% to 38% (40,42,44,64–71). An evaluation of the IDOL-consortium involving 10 centres across the US, ITBL was present in 12%, ranging from 6% to 26% in the individual centres (72). Identified risk factors for ITBL are prolonged duration of warm and cold ischemia and specifically the length of donor warm ischemia. There is no consensus about the impact of donor age and development of ITBL and these grafts should not be avoided for age per se (45,46,66,73,74).

Acute kidney injury

AKI is a common issue after liver transplantation and is the result of donor, surgical and recipient risk factors. The kidney is a known organ to suffer from hepatic IRI, due to the release of pro-inflammatory cytokines and reactive oxygen species, acting like a systemic inflammatory response syndrome (75). With the evolving use of marginal grafts, including DCD grafts, graft quality takes more part in the development of post-transplant AKI (76). The Birmingham group was the first to describe an increased frequency of AKI with the use of DCD grafts and was observed in 53% of the recipients, compared to 32% of the DBD recipients (**Figure 5**) (77). These findings were later confirmed by others (54). The increased incidence of AKI did not lead to more CKD in the Birmingham cohort. However, an indirect relationship between DCD liver transplantation and end-stage renal disease on the long-term was observed in a nationwide-US registry study (78).

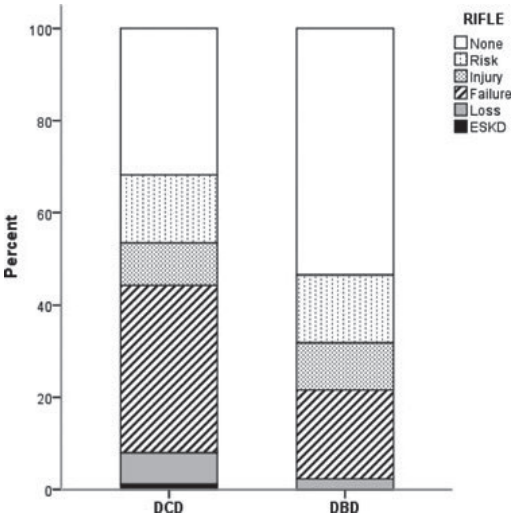

Figure 5 – Comparison of acute kidney injury after liver transplantation using DCD or DBD grafts. From Leithead et al, American Journal of Transplantation, 2012 (77).
Stacked bar graph demonstrating the proportion of DCD liver transplant recipients and DBD recipients who developed acute renal dysfunction during the immediate postoperative period.

Cost-Effectiveness & Quality of Life

The use of DCD grafts is also associated with higher costs after transplantation, due to the development of complications requiring multiple interventions, hospital admissions and even retransplantation, such as ITBL (79). This has been shown in several cost-effectiveness studies from US and the Netherlands (80,81). Due to the long-term problems with intensive and multidisciplinary treatments, ITBL has a significant impact on the quality of life of the patients as well (82). Recipients of DCD grafts have a significant better quality of life on the long-term, when compared to recipients who remained waiting on the waiting list for a DBD liver transplant (83).

Although DCD liver transplantation is not without risk, it has expanded the donor pool significantly over the last years. Avoiding the DCD-specific complications and preventing the need for retransplantation are the most important issues to solve in the near future to improve outcomes and quality of life and reduce costs. Machine perfusion techniques have the potential to improve outcomes of marginal grafts, such as DCD grafts and assessment of the risk factors for graft failure in DCD liver transplantation is pivotal to identify these grafts that have the most benefit of these new preservation techniques (84).

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