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ORIGINAL ARTICLE

Liver transplantation from donation after cardiac death donors: initial Belgian experience 2003–2007

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Abstract

The Belgian experience with donation after cardiac death (DCD) liver transplantation (LT) was retrospectively reviewed, particularly evaluating patient and graft survivals, and biliary complications. From 2003 to 2007, 58 DCD-LT were performed in Belgium. Mean procurement total warm ischemia time was 25 ± 2 min (mean ± SEM). Mean cold ischemia time was 451 ± 18 min. Mean follow-up was 23 ± 2.2 months. Post-transplant peak aspartate aminotransminases was 2241 ± 338 UI/l. Patient survivals at 1 month, 1 and 3 years, were 91.3%, 83.3% and 66.9% respectively. Graft survivals at 1 month, 1 and 3 years, were 84.4%, 72.4% and 48.8% respectively. Two patients (3.4%) developed primary nonfunction. Regarding the biliary complications, seven grafts (12%) were lost because of intrahepatic cholangiopathy, and 12 other patients (20.6%) developed bile duct stenoses requiring endoscopic and/or surgical management. The rate of symptomatic ischemic biliary lesions for grafts surviving more than 3 months was 38% (19/50). Although DCD organ donors may be a source of viable liver grafts, results were inferior to those obtained with donation after brain death LT in this series. Prognostic criteria have to be developed to improve results of DCD-LT.

Introduction

The excellent results of liver transplantation (LT) have led to an increasing discrepancy between the number of potential LT recipients and the available donation after brain death (DBD) liver donors. Alternative sources of liver grafts have been developed to overcome this organ shortage somehow, including living liver donors, split liver grafts, extended criteria DBD donors, and donation after cardiac death (DCD) donors [1,2]. Contrary to DBD donors, in DCD donation, death is diagnosed on the basis of cardiovascular criteria, after cessation of the blood flow during a sufficient time allowing to determine cardiovascular death [3]. DCD donation imposes thus an additional warm ischemic injury prior to organ preservation by cooling and flushing. This supplementary insult may increase the rate of graft failure because of primary non-function (PNF) and ischemic type biliary lesions (ITBL) [4].

In 1995, the Maastricht conference defined four categories of DCD donors [5]. Practically, in LT, DCD donors may be classified as uncontrolled or controlled. In uncontrolled DCD donors, the cessation of cardiopulmonary

function is an unplanned event that may occur outside the hospital (Maastricht category I) or within the hospital (Maastricht category II). In controlled DCD donors (Maastricht category III), cessation of cardiovascular activity may be planned in a patient with severe and irreversible cerebral lesions in whom intensive care is deemed futile by the medical team in charge, independently of any organ donation. When medical decision of care withdrawing is confirmed to the patient's next of kin, the possibility of DCD donation and the patient's willingness for after death organ donation may be discussed. DCD procedure may be planned with donor extubation either in the intensive care unit (ICU) or in the operating room. In this controlled DCD, procurement warm ischemic injury may be minimized by the presence of the organ procurement surgical team ready for rapid after death organ retrieval. The Maastricht category IV DCD donors constitute a small group of DBD organ donors who developed unexpected cardiac arrest just before or during organ procurement.

With the increasing donor organ shortage, the use of DCD liver grafts has been increasingly reported. Programs of Maastricht category III DCD-LT have been developed in the United-States as well as in Western Europe and some centers even developed DCD-LT programs using Maastricht category II livers [6]. Good results of Maastricht category III DCD-LT, comparable to the results of DBD-LT, have been reported [7–10]. However, most centers, as well as the reports from the United Network for Organ Sharing (UNOS) network registry, demonstrated an increased risk for liver graft failure [11–18]. After the initial and successful development of DCD renal transplantation in the Netherlands and Belgium, programs of liver, lung or pancreatic islet transplantation were initiated [19–21]. The aim of this retrospective study was to evaluate the results of the Belgian multicenter experience in DCD-LT, in terms of patient and graft survivals, and of ITBL. The authors also intended to determine the donors' characteristics and the transplant variables that may be linked to the results of DCD-LT.

Patients and methods

This study was a retrospective review of the Belgian experience with DCD-LT during the period from 2003 to December 2007, and is an extension of a preliminary report on the 2003–2005 period [19]. DCD donation has been initiated in all Belgian transplant centers after approval by the different institutional committees, and the Belgian National Council of Physicians [21]. The Belgian LT community is composed of six active transplant centers sharing a common pool of organ donors and a national waiting list with a patient-oriented liver graft allocation performed by the Eurotransplant organization. These centers are responsible for the liver graft procurements within their regional area. The first Belgian DCD-LT were performed in 2003 [19], and all six Belgian LT centers had active DCD-LT program by 2008. A DCD-LT registry was created by the Belgian Liver Intestinal Committee, a section of the Belgian Transplant Society. Complete follow-up was obtained up to December 31, 2007, in a retrospective manner. Mean follow-up was 23 ± 2.2 months (range, 1–60 months). No patient was lost to follow-up.

From 2003 to December 2007, 58 DCD-LT were performed in Belgium, representing 4.7% of the 1239 Belgian LT activity in the same period. Fifty-six were from Maastricht category III donors and two from category IV. No category II DCD-LT was performed despite active category II DCD procurement programs in some Belgian centers. For category III donors, withdrawal of life support and extubation were performed by a nontransplant physician in the operative room in all cases. Intravenous heparin was given in most cases before cessation of circulation. Organ recovery started 2–5 min after declaration of death, by cannulation of the femoral vessels or by rapid midline laparotomy and sternomy with caval and aortic cannulation. Once the cold flush with university of Wisconsin (UW) or histidine–tryptophan–ketoglutarate (HTK) solutions was initiated, the aorta was cross-clamped in the chest just above the diaphragm, whereas the abdominal and thoracic cavities were filled with iced fluid for topical cooling. After completion of the aortic flush, the organs were removed and stored in a standard manner until transplantation.

Donation after cardiac death liver grafts were considered as marginal grafts, and were allocated in a center-oriented manner to shorten cold ischemia time (CIT). The recipients were chosen according to the urgent need for transplantation and his (her) chances to receive a liver graft in a timely manner according to the regular patient-oriented rules, and this included patients with extended criteria hepatocarcinoma. If no adequate candidate was available, the DCD liver graft was offered to other centers in Belgium and the Netherlands, two Eurotransplant countries allowing DCD procurement.

In all DCD donors, age, gender, cause of brain damage, terminal blood sodium level, terminal liver function tests, need of vasopressors, length of the ICU stay, body mass index (BMI), last 24-h diuresis, past cardiopulmonary resuscitation, were collected. In the recipients, age, gender, LT indication, status 1 or hyper urgent (HU) status, last laboratory model for end-stage liver disease (MELD) score before transplantation, were recorded. The use of heparin in the donor, the type of preservation solution (UW or HTK), and the exchange between centers that

transplanted but not procured DCD liver grafts, were also noted.

Donor total warm ischemia time (DTWIT) was defined as the time between discontinuation of mechanical ventilation and initiation of aortic perfusion with the cold preservation solution [22]. DTWIT was divided into two separate phases, the time of life-support withdrawal to cardiac arrest (withdrawal phase), and the time between cardiac arrest to aortic cannulation (acirculatory phase), as proposed [3]. CIT was defined as the time from aortic cold perfusion until reperfusion of the liver graft in the recipient. Procurement time was defined as the time from aortic cold perfusion to placement of the liver graft in iced preservation fluid. Suture time was defined as the time from removing the liver graft from the iced preservation fluid to revascularization of the graft.

Primary endpoints of this retrospective study were graft and patient survivals. Graft survival was defined as time from LT to graft loss and/or patient death. Patient survival was considered from first transplantation to patient death. To estimate better the risks of DCD-LT, we calculated graft and patient survivals censored for recipient death unrelated to the quality of the graft (malignant tumor, accident), as a secondary endpoint. Secondary endpoints were also early death (<3 months post-OLT), first week peaks of transaminases and total bilirubin, occurrence of PNF, hepatic artery thrombosis (HAT), length of the ICU and hospital stays, and need for retransplantation. The overall rate of symptomatic intra- and extra-hepatic biliary complications requiring invasive (endoscopy, surgical hepaticojejunostomy or retransplantation) management, was also studied, excluding grafts lost within 3 months from causes unrelated to biliary problems.

Data are presented as means ± standard error of the mean (SEM). Means were compared with Student *t*-test, and proportions were compared with Fischer's or chi-square test, when appropriate. Survival rates were estimated with the Kaplan–Meier method. Linear regression was used to link the different times of the transplant procedures, to the level of peak transaminases and total bilirubin. A value of $P < 0.05$ was considered significant. Data were analyzed using the INSTAT 3.0b and PRISM 5 softwares for Macintosh (GraphPad Software, San Diego, CA, USA).

Results

Donor baseline characteristics

The characteristics of the DCD donors are presented in Table 1. Donors were mostly men, and their mean age was 44.6 ± 1.9 years. Trauma was the main cause of irreversible brain damage leading to withdrawal of medical support; four patients who were waiting medical-assisted death or euthanasia according to the Belgian law, requested after-death organ procurement. Mean ICU stay before withdrawal was 4.8 ± 0.5 days. Liver tests were at the upper limit of normal values.

Table 1. Baseline donors' characteristics.

	Data	Range
Age (years)	44.6 ± 1.9	13–71
Female (%)	32.7	
CPR (%)	25.8	
Causes of death (*n*)		
Anoxia	14	
Trauma	23	
Cerebrovascular accident	17	
Other (euthanasia)	4	
BMI (kg/m^2)	24.5 ± 0.5	18–38
Intensive care stay (days)	4.8 ± 0.5	0–19
Urinary output (ml/day)	3002 ± 266	980–8450
Pressors (%)	44.8	
Na (mmol/l)	142.3 ± 0.8	129–164
Total bilirubin (mg/dl)	0.53 ± 0.04	0.11–1.3
AST (U/l)	50.5 ± 5.7	10–300
GGT (U/l)	59.8 ± 12.1	3–606

CPR, cardiopulmonary resuscitation; BMI, body mass index; AST, aspartate aminotransferase; GGT, gamma glutamil transferase.

Recipient baseline characteristics

Recipients' mean age was 54.9 ± 1.5 years (range, 10–70 years). Indication for LT was end-stage cirrhotic liver disease in 26 patients (viral: 8, alcohol-related: 12, primary biliary cirrhosis: 2, others: 4), hepatocellular cancer in 22 patients (cirrhotic livers: 20, noncirrhotic livers: 2), and miscellaneous in five cases (primary sclerosing cholangitis: 2, familial amyloid polyneuropathy: 1, neurendocrine liver metastases: 1, biliary atresia: 1). Additionally, in five cases, DCD LT was performed for HU patients (Eurotransplant equivalent to UNOS status 1a) for fulminant hepatic failure (2), liver failure after resection for Klatskin tumor (1) and urgent retransplantation after failed first transplantation (2). Mean lab MELD score at transplantation was 15.4 ± 1 (range, 6–37).

DCD procurement and LT characteristics

The characteristics of the DCD procurements and LT are presented in Table 2. Heparin was administrated in more than 80% of the DCD donors before cardiac arrest. HTK preservation solution was used in 65% of the cases. Thirty-eight DCD grafts were allocated within the procuring center. Twenty DCD liver grafts were exchanged between centers; 15 were shipped from other Belgian centers (national allocation) and five from the Netherlands

Table 2. Characteristics of the procurement and transplantation of the DCD grafts.

	Data	Range
Heparin (%)	82.7	
HTK/UW (*n*)	38/20	
Graft origin L/N/I (*n*)	38/15/5	
DTWIT (min)	25.18 ± 2.2	10–109
Withdrawal phase (min)	14.75 ± 2.09	4–98
Acirculatory phase (min)	10.6 ± 0.84	4–38
Procurement time (min)	42.5 ± 3.1	15–92
CIT (min)	451 ± 18	148–770
Suture time (min)	50 ± 2.3	25–135

DCD, donation after cardiac death; DTWIT, donor total warm ischemia time; CIT, cold ischemia time; HTK, histidine–tryptophan–ketoglutarate solution; UW, University of Wisconsin solution; Graft origin: L, local; N, national; I, international.

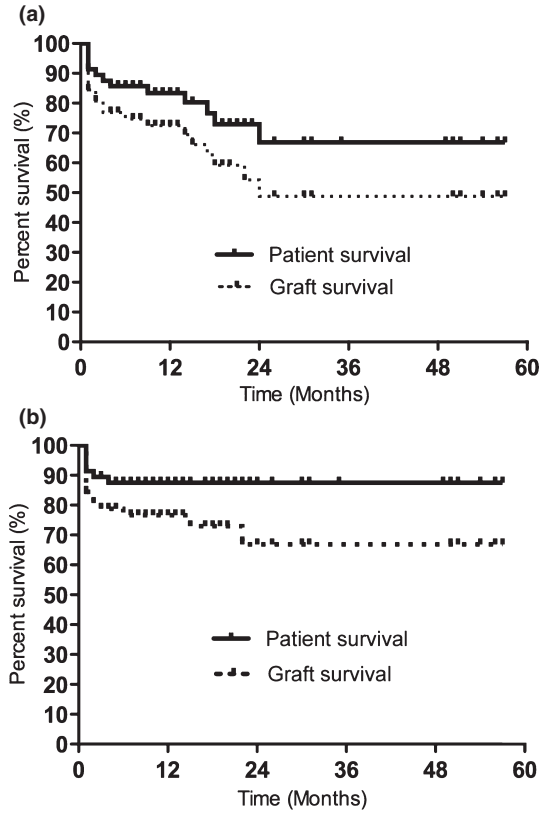

Figure 1 Patient and graft survivals according to the Kaplan–Meier curves. (a) Global survival curves. (b) Survival curves censored for patients who died of cancer or trauma.

(international allocation). Mean DTWIT was 25.18 ± 2.2 min, and mean CIT was 451 ± 18 min.

Primary end-points

Overall graft and patient survival rates are presented in Fig. 1a. One-month-, 1-year- and 3-year-patient survivals were 91.3%, 83.3% and 66.9%, respectively. One year- and 3-year-graft survivals were 84.4%, 72.4% and 48.8%, respectively. Causes of early death (<3 months) were perioperative cardiac failure in two cases, PNF in one case, acute respiratory distress syndrome in one case, multiple organ failure in one case, and liver insufficiency with HAT in one case. Eight other patients died later, one from intractable biliary sepsis while waiting retransplantation, five from cancer (melanoma: 1, lymphoma: 1, donor transmitted sarcoma: 1, hepatocarcinoma recurrence: 2) and two from violent death (car accident and suicide). Eight patients underwent retransplantation, two urgently for PNF ($n = 1$) and HAT ($n = 1$), and six for intractable biliary stenoses, one at month six post-transplant after HAT surgically revascularized at post-transplant day 7. One of the patients who underwent late retransplantation, died from lymphoma at postoperative month 7. In total, 21 DCD liver grafts were lost for reasons of retransplantation or death at follow-up (Table 3).

In univariate analysis, the relationship between characteristics of the donors, the recipients and the transplant procedures, and global graft and patient survivals as primary endpoints, showed a tendency to a higher risk of graft and patient loss in case of CIT longer than 6 h, and in case of withdrawal phase of the procurement exceeding 15 min (Table 4). There was a tendency to a lower risk of graft failure if DTWIT was inferior to 20 min (Table 4).

Postoperative evolution and secondary end-points

Six patients (10.3%) who certainly died of causes unrelated to the graft quality (malignant tumor and accident) and who did not undergo retransplantation, were excluded for calculation of censored-patient and graft survival (Fig. 1b). One- and 3-year-censored patient survivals

Table 3. Causes of the 21 losses of DCD hepatic grafts during follow-up.

Causes of graft loss	*n*	Outcome	Link to DCD donation
PNF	2	1 death, 1 reTx	Probable
Operative death	2	2 deaths	Possible
Hepatic artery thrombosis	2	1 death, 1 reTx	Possible
ARDS, MOF	2	2 deaths	Possible
Diffuses intrahepatic stenoses	7	1 death, 6 reTx*	Highly probable
Unrelated death	7	7 deaths†	None

DCD, donation after cardiac death; PNF, primary non function; re Tx, retransplantation; ARDS, acute respiratory distress syndrome; MOF, multiple organ failure.

*One patient underwent retransplantation for intrahepatic stenoses 6 months after successful surgical hepatic artery revascularization.

†One patient died of lymphoma 6 months after retransplantation for intrahepatic bile duct stenoses).

Table 4. Univariate comparison between the primary end-points and different factors linked to the donor, the recipient or the transplantation procedure.

	Death			Graft failure		
Factors	*P*	Risk ratio	95% CI	*P*	Risk ratio	95% CI
Donor						
Donor age <50 years	0.37	0.864	0.652–1.145	0.41	1.227	0.815–1.847
ICU <5 days	1	1.037	0.376–2.853	0.76	0.91	0.637–1.31
Cause of death	0.5			0.13		
BMI<25 kg/m^2	0.75	1.218	0.4383–3.384	1	0.986	0.677–1.437
Cardiac arrest (yes versus no)	0.32	0.478	0.12–1.894	0.21	0.44	0.14–1.386
Donor inotropes (yes versus no)	1	1.031	0.427–2.488	1	0.932	0.509–1.708
Donor AST <50 U/l	0.35	1.786	0.563–5.659	0.77	1.101	0.768–1.578
Donor GGT <50 U/l	1	1.063	0.386–2.921	0.55	1.143	0.819–1.594
Transplantation						
Graft allocation (L/N/I)	0.12			0.24		
Heparin (yes versus no)	0.1	0.383	0.163–0.899	0.14	0.798	0.596–1.069
DTWIT <20 min	0.48	0.589	0.189–1.833	0.06	0.506	0.233–1.097
DTWIT <30 min	0.39	0.585	0.192–1.783	0.43	0.875	0.639–1.197
Withdrawal phase <10 min	0.5	0.63	0.245–1.623	0.76	0.875	0.427–1.793
Withdrawal phase <15 min	0.02*	0.725	0.502–1.048	1	0.959	0.67–1.371
Acirculatory phase <10 min	1	0.889	0.286–2.757	0.14	0.685	0.423–1.108
Acirculatory phase <15 min	0.5	0.706	0.276–1.803	0.16	0.845	0.67–1.067
Flush solution (HTK/UW)	0.1	0.408	0.177–0.936	0.47	0.881	0.671–1.155
Procurement time <45 min	1	1.032	0.392–2.712	0.37	0.761	0.45–1.289
CIT <6 h	0.08	0.288	0.067–1.24	0.04*	0.463	0.207–1.035
CIT <10 h	1	1.347	0.208–8.685	1	1.003	0.829–1.214
Suture time <60 min	0.7	0.814	0.268–2.471	1	1.039	0.809–1.333
Recipient						
Age recipient <50 years	0.71	1.385	0.518–3.696	0.35	1.636	0.662–4.04
MELD <15	0.32	1.877	0.57–6.17	0.54	1.184	0.758–1.849
HU	0.07	3.18	1.283–7.884	0.34	2.571	0.466–14.171
Center	0.9			0.46		

ICU, intensive care unit; BMI, body mass index; AST, aspartate aminotransferase; GGT, gamma glutamil transferase; L, local; N, national; I, international; DTWIT, donor total warm ischemia time; CIT, cold ischemia time; MELD, model for end-stage liver disease score; HU, high urgency status; HTK, histidine–tryptophan–ketoglutarate solution; UW, University of Wisconsin solution. *$P < 0.05$.

were 87.5%; 1- and 3-year-censored graft survivals were 76.6% and 66.8%, respectively.

Postoperative mean peak AST was 2242 IU/l ± 338 (range, 34–10 505 IU/l) and mean peak total bilirubin was 6.76 ± 0.93 mg/dL (range, 0.77–29.6 mg/dL). Considering early post-LT death, results were significantly lower in urgent LT (Table 5). There was a trend for a correlation between the length of CIT and the post-transplant peak AST (slope: 4.63; *r*: 0.253; $P = 0.06$). No other significant correlation was demonstrated between DTWIT, CIT, DTWIT added to CIT, procurement time and suture time and post-transplant peaks of AST or bilirubin. For patients surviving the first month, mean ICU and hospital stays were 6.98 ± 1.22 days (range, 1–46 days) and 33.81 ± 5.06 days (range, 10–213 days), respectively.

In addition to the seven DCD (12%) liver grafts lost for reasons of diffuse intrahepatic stenoses (one death and six retransplantations), 12 (20%) other patients developed ITBL requiring endoscopic and/or surgical management. Censoring the eight DCD graft losses within the first 3 months (six early deaths and two early retransplantations for PNF and HAT), the overall rate of symptomatic bile duct lesions was 38% (19/50). We could not identify clear risk factors for ITBL (Table 5). Unexpectedly, donor age over 50 years and gamma glutamyl transferase superior to 50 U/l were significantly associated with a decreased risk of bile duct problems, but this result is probably not medically relevant.

Discussion

This retrospective study on the Belgian experience in DCD-LT shows that controlled Maastricht category III DCD donors constitute a potential source of liver grafts that may partially help fill the gap between the needs for LT and the overall DBD liver graft pool. However, this

Table 5. Univariate analysis comparing the secondary end-points and different factors linked to the donor, the recipient or the transplantation procedure.

	Early death			Censored graft failure			Biliary complications		
Factors	*P*	Risk ratio	95%	*P*	Risk ratio	95%	*P*	Risk ratio	95%
Donor									
Donor age <50 years	0.225	1.507	1.025–2.217	0.533	1.209	0.8–1.826	0.018*	1.842	1.132–2.997
ICU <5 days	0.683	0.857	0.439–1.671	0.311	0.761	0.469–1.237	0.521	1.145	0.817–1.604
Causes of death	0.684			0.365			0.294		
BMI<25 kg/m^2	0.407	1.325	0.92–1.907	0.757	1.084	0.731–1.607	0.362	1.257	0.836–1.889
Cardiac arrest (yes versus no)	0.178	NA	NA	0.086	0.224	0.032–1.559	0.11	0.381	0.123–1.176
Donor inotrope (Yes versus No)	0.69	1.59	0.39–6.47	0.525	1.393	0.711–2.725	0.386	0.704	0.324–1.53
Donor AST <50 U/l	1	1.218	0.259–5.714	0.757	0.942	0.607–1.463	1	1.068	0.723–1.578
Donor GGT <50 U/l	0.661	2.55	0.331–19.612	0.189	1.316	0.969–1.788	0.025*	1.599	1.103–2.318
Transplantation									
Type of allocation (L, N, I)	0.567			0.565			0.55		
Heparin (Yes versus No)	0.338	0.51	0.114–2.27	0.690	0.934	0.69–1.264	0.695	0.915	0.696–1.205
DTWIT <20 min	0.661	0.615	0.112–3.373	0.164	0.521	0.195–1.395	1	0.96	0.536–1.717
DTWIT <30 min	1	0.952	0.118–7.627	0.646	0.937	0.67–1.31	0.679	0.933	0.695–1.253
Withdrawal phase <10 min	0.645	0.54	0.12–2.436	0.713	0.74	0.276–1.985	0.754	1.145	0.564–2.323
Withdrawal phase <15 min	0.115	0.235	0.054–1.025	0.669	0.86	0.526–1.406	0.295	0.789	0.512–1.216
Acirculatory phase <10 min	0.625	0.444	0.049–3.979	0.184	0.655	0.353–1.215	0.365	0.789	0.511–1.217
Acirculatory phase <15 min	1	0.973	0.111–8.505	0.328	0.909	0.711–1.163	1	1.014	0.873–1.178
Flush solution (HTK/UW)	0.591	0.52	0.117–2.316	1	1.048	0.811–1.352	0.451	1.128	0.886–1.436
Procurement time <45 min	0.672	0.666	0.149–2.98	0.177	0.625	0.308–1.265	0.746	0.919	0.577–1.464
CIT <6 h	0.358	0.288	0.034–2.422	0.513	0.682	0.289–1.608	0.555	1.291	0.739–2.254
CIT<10 h	1	NA	NA	0.096	1.364	1.143–1.626	1	1.031	0.828–1.283
Suture time <60 min	1	1.209	0.147–9.897	1	1.019	0.763–1.36	0.235	0.821	0.611–1.105
Recipient									
Age recipient <50 years	0.18	0.385	0.098–1.507	0.267	1.964	0.765–5.038	0.487	1.526	0.509–4.57
MELD <15	0.375	0.444	0.082–2.402	0.312	0.711	0.355–1.422	0.733	1.116	0.716–1.738
HU	0.01*	7.95	2.434–25.964	0.094	4.5	0.829–24.424	1	1.4	0.092–21.092
Center	0.07			0.015*			0.052*		

ICU, intensive care unit; BMI, body mass index; AST, aspartate aminotransferase; GGT, gamma glutamil transferase; L, local; N, national; I, international; DTWIT, donor warm ischemia time; CIT, cold ischemia time; MELD, model for end-stage liver disease score; HU, high urgency status; HTK, histidine–tryptophan–ketoglutarate solution; UW, University of Wisconsin solution. *$P < 0.05$.

series also demonstrates an overall inferior DCD liver graft survival (49% at 3 years). Moreover, the biliary complications rate of grafts that did not fail within the first 3-month post-LT was already 38% in this series after a relatively short follow-up of 23 months. These results are in accordance with the higher risk of biliary complications and graft loss in DCD-LT, as reported in earlier studies [23].

Most of the Belgian DCD liver grafts originated from Maastricht category III DCD donors. Despite active category II DCD kidney procurement programs in some Belgian centers, such donors were not used for liver graft donation within the study period. In Maastricht category III donation, cessation of life support is a planned event in which the period between cessation of ventilation and cardiac arrest and aortic flushing, might be easily monitored. Moreover, the presence of the procurement team at the time of life support withdrawal, allows to limit donation DTWIT to a minimum. For these reasons, Maastricht category III DCD donation has also been called 'controlled' DCD. On the contrary, in uncontrolled DCD donors, the cessation of cardiopulmonary function is an unplanned event that may occur outside the hospital (Maastricht category I) or within the hospital (Maastricht category II). The procurement DTWIT is therefore longer and difficult to define in uncontrolled DCD, increasing the risks for ischemic failure of the graft. The results of this study will certainly not favor the extension of controlled DCD-LT to an uncontrolled DCD-LT activity in the next years in Belgium.

A particularity of DCD donation in Belgium consists of the possibility of after death procurement in individuals who required euthanasia as allowed by the Belgian law [24]. Belgium was the second country in the world after the Netherlands to legalize medically assisted death or euthanasia under very strict conditions [24]. Four

patients who suffered from severe neurological diseases and who were granted euthanasia required that procurement of their organs should be performed after their death. These procurements were allowed by the ethical committees of the institution where the euthanasia procedures were performed [25]. As these procedures included a planned and medically controlled cardiopulmonary arrest, they were naturally classified in the Maastricht category III donation category.

In this series, we, as others [3,12,17,18,22,26–30], used the definition of DTWIT as the interval between discontinuation of donor mechanical ventilation to the aortic perfusion with the cold preservation solution. DTWIT may be divided into two separate phases, the time from life-support withdrawal to cardiac arrest (withdrawal phase), and the time from cardiac arrest to aortic cannulation (acirculatory phase), as described by the 2006 American consensus report [3]. This definition of the DCD procurement DTWIT is imperfect, but has the merits to be simple and useful for comparison of studies. During the circulatory arrest phase, warm ischemia is complete as no cardiac flow and pulmonary function are observed. During the withdrawal phase, warm ischemia is only partial as this period is marked by varying periods of hypotension and hypoxia before the cessation of all cardiopulmonary function. Some authors used alternative definitions of warm ischemia, e.g. mean or systolic arterial pressure lower than 60 mmHg [22], 50 mmHg [16] or 35 mmHg [31] and/or oxygenation saturation <70% [7,32], 60% [16] or 35% [31], or mean arterial pressure <30 mmHg and/or oxygen saturation <25% [17,31]. Clearly, there is a need for a consensus in this matter. Practically, we consider that these data are very often impossible to trace back precisely, especially in a retrospective multicenter study. Moreover, oxygen saturation is often difficult to monitor noninvasively during DCD donation once its value is below 80%, as pulse oxymeters are not calibrated to low oxygen saturation and premortem vasoconstriction does not always allow reliable recordings.

This multicenter Belgian study showed overall 3-year patient and graft survival rate of 66.9% and 48.8%, respectively. This series was comparable to the other reports on DCD-LT in literature in terms of DTWIT and CIT [7,17,18,23,31,32]. One-year graft and patient survivals were quite equivalent to other reported series. However, our 3-year results are worse than previously reported, a feature which may be related to the particular high rate of deaths caused by events unrelated to DCD procurement such accident and cancer, and by the high rate of retransplantation.

Overall, 38% of DCD grafts surviving 3 months developed ITBL, a rate of biliary complications higher than usually expected in DBD-LT. This is probably explained by the addition of donation DTWIT to CIT. A withdrawal phase of more than 15 min was significantly related to an increased risk of post-transplant death, and a CIT of more than 6 h was linked to graft failure. These results are consistent with data in the literature, indicating that in DCD-LT, both warm and CIT must be limited to a minimum. We were not able to indentify in this series other compromising factors for DCD-LT results. This is probably linked to the fact that LT results depend on multiple donor and recipient variables and that a higher case load is necessary to find out compromising factors.

In this multicenter Belgian experience, 1- and 3-year-graft survivals, censored for accidental or cancerous patient's death, were 87.5% and 66.8%, respectively. These results mean that even in this preliminary experience, two-third of the DCD liver grafts may provide a chance to receive a life-saving graft. This is an important message in the current era of organ donor shortage and too high rate of death on the waiting lists. Better knowledge of the risks of DCD-LT failure, and particularly a limitation of the warm and cold ischemia, may offer better results in the future.

In recent reports, it was suggested that DCD donor age of more than 40 or 50 years and ICU stay of more than 5 days, may be risk factors for post-transplant DCD-LT failure [17]. Our results, as others [31], did not support these findings. Similarly, we did not experience an early increased graft failure from viral recurrence in hepatitis C virus positive patients (data not showed), as described by others [30].

In conclusion, the multicenter Belgian experience with DCD-LT confirmed that DCD liver grafts carry an increased risk of graft failure. Overall results were inferior to what should be expected in the modern era of LT, with one-half of the grafts lost at 3 years. Procurement DTWIT beneath 30 min and CIT beneath 6 h seem to be related to better outcome. Further improvements are needed to allow wider and safer use of DCD liver grafts. For the time being, these grafts should be carefully used in informed patients, in whom current allocation scheme does not provide sufficient chances to be transplanted with a regular DBD graft in a timely manner.

Authorship

O. Detry designed the study and wrote the manuscript. All authors are active Belgian liver transplant surgeons who were clinically involved in the procurements and transplantations reported in this paper. All authors participated in the data collection, and all approved the final version of the manuscript.

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