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Asystole to cross-clamp period predicts development of biliary complications in liver transplantation using donation after cardiac death donors

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Summary

This study sought to determine the procurement factors that lead to development of intrahepatic bile duct strictures (ITBS) and overall biliary complications in recipients of donation after cardiac death (DCD) liver grafts. Detailed information for different time points during procurement (withdrawal of support; SBP < 50 mmHg; oxygen saturation <30%; mandatory wait period; asystole; incision; aortic cross clamp) and their association with the development of ITBS and overall biliary complications were examined using logistic regression. Two hundred and fifteen liver transplants using DCD donors were performed between 1998 and 2010 at Mayo Clinic Florida. Of all the time periods during procurement, only asystole-cross clamp period was significantly different between patients with ITBS versus no ITBS ($P = 0.048$) and between the patients who had overall biliary complications versus no biliary complications ($P = 0.047$). On multivariate analysis, only asystole-cross clamp period was significant predictor for development of ITBS ($P = 0.015$) and development of overall biliary complications ($P = 0.029$). Hemodynamic changes in the agonal period did not emerge as risk factors. The results of the study raise the possibility of utilizing asystole-cross-clamp period in place of or in conjunction with donor warm ischemia time in determining viability or quality of liver grafts.

Introduction

Donation after cardiac death (DCD) has been recognized as an important source of organs for liver transplantation (LT). DCD organs could help fill the gap between the demand and supply of liver grafts [1,2]. DCD donors are a specific type of donors in which declaration of death is based upon cardiopulmonary criteria rather than cessation of brain and brainstem function. The reported outcomes with this type of liver grafts have been inferior in comparison with those from donation after brain dead (DBD) liver grafts [3–5]. The DCD procurement subjects the liver graft to warm ischemia, which results in increased rates of primary nonfunction (PNF), hepatic artery thrombosis (HAT), and particularly ischemic cholangiopathy (IC). IC can lead to intrahepatic bile duct strictures (ITBS), hepatic abscesses, and hepatic necrosis resulting in graft loss. In comparison with donation after brain death (DBD) donors, DCD liver grafts are considered as high risk because of the overall increased rates of graft loss and long-term morbidity, mostly related to the consequences of IC [4–6]. As a result, there is reluctance in the transplant community to use DCD liver grafts. This reluctance, coupled with the probability that the donation pattern will change from DBD to DCD, provide a strong incentive for the transplant community to identify the mechanisms underlying suboptimal function of DCD grafts and thereby focus efforts to improve the outcome [7]. Previous publications from single centers sought to identify the risk factors for developing complications in DCD grafts as well as how to delineate the care for patients who experienced these complications, particu-

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larly ITBS [4,5]. The United Network for Organ Sharing (UNOS) registry provides data from large number of transplants. However, because of data heterogeneity and especially lack of registry data on specific events at the time of procurement, there is an incomplete understanding of reasons that lead to development of ITBS and extrahepatic biliary complications in DCD liver grafts [3]. A commonly used parameter of DCD graft injury is the donor warm ischemia time (DWIT). However, the DWIT is a composite measure and is too crude to discriminate among the component timeframes with respect to graft function. Significant variation occurs among DCD donors with respect to systemic and hepatic hemodynamics, oxygen transport, and consumption following withdrawal of life support until the infusion of cold preservation solution [8]. Individual events during DCD procurement, such as variations in hemodynamics, mandatory wait period, or time from incision to cannulation of aorta and cross clamp, all included in DWIT, may have different impact on the outcome of the liver graft.

This retrospective analysis from a single institution with a large DCD experience was undertaken to analyze events during procurement as potential risk factors for development of ITBS and overall biliary complications. We hypothesize that timeframes of discrete events (hypotension, hypoxia, and absence of circulation) during DCD liver graft procurement correlate with an increased risk of developing ITBS and overall biliary complications. We present new data and analyses related to the procurement timeline and hemodynamic changes from withdrawal of life support till aortic cross-clamp. This report builds on our previous report assessing risk factors for development of ITBS and graft loss [9].

Methods

This is a retrospective review of LT using grafts from DCD donors performed between December 1998 and December 2010 at Mayo Clinic in Jacksonville, FL. Approval for the study was obtained from the Mayo Clinic Institutional Review Board. The study was performed by chart review of all liver transplants utilizing DCD organs during the same time period. Recipient information included; age, gender, calculated Model for End-stage Liver Disease (MELD) score at the time of transplant, and follow-up time.

Detailed information regarding the DCD donors was obtained from the Mayo Clinic Florida procurement database. Donor information included age, gender, share status (geographic location), cause of death, individual time points of events during DCD procurement, cold ischemia time (CIT), warm ischemia time during implantation (WIT), donor risk index (DRI), and individual components of DRI. All DCD donors were classified as Maastricht type 3 (controlled awaiting cardiac death) [10]. For DCD donors, DWIT was defined as the time from withdrawal of both ventilator and cardiac support to the time of aortic cross clamping (immediately after start of cold perfusion of the organ). CIT was defined as the time from infusion of cold preservation solution until portal reperfusion of the liver in the recipient. Detailed information for different time points during procurement (withdrawal of support; SBP <50 mmHg; oxygen saturation <30%; mandatory wait period; asystole; incision; aortic cross clamp) were collected (Fig. 1). Durations between specific events were then retrospectively calculated to delineate the effect of hypotensive warm ischemia, hypoxic warm ischemia, and absence of circulation. Primary outcomes were ITBS and overall biliary complications in recipients of DCD grafts. Other major complications, such as PNF, HAT, and patient and graft survival were recorded.

Surgical techniques

In DCD donors, withdrawal of support, institution of comfort measures, and declaration of death were in strict compliance with local Organ Procurement Organizations (OPO) and donor hospital policies. At no time was the transplant team involved in the withdrawal process or in advising how it should occur. After consent was obtained, the patient was taken to either a preoperative holding area or brought to the operating room with full cardiopulmonary support in place. An independent physician from the donor hospital, separate from the OPO and the transplant center, was assigned to withdraw artificial life support and provide end of life care to the patient. Blood pressure (invasive with arterial line or noninvasive with blood pressure cuff, depending on local hospital practices) and oxygen saturation (noninvasive) were recorded at 1-min intervals. Following the declaration of death by the independent physician, a further 2 or 5 min of mandatory observation was performed as described in the 1997 Institute of Medicine Guidelines [11]. Heparin was

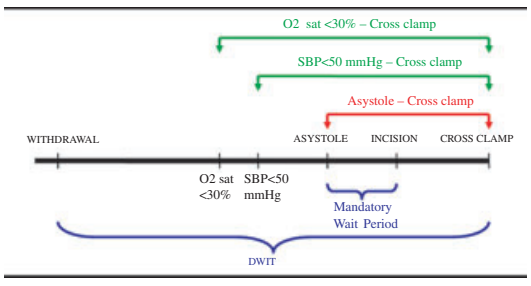

Figure 1 Different time points during procurement.

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administered to the patient according to the donor hospital policy. Following the mandatory wait period, a rapid retrieval technique was performed in which the abdomen was opened with a cruciate incision [9]. The small bowel was reflected superiorly and the aorta was cannulated. The intra-thoracic descending aorta was cross-clamped either through a median sternotomy or through the left hemi-diaphragm immediately after the start of cold perfusion. The suprahepatic inferior vena cava was opened to allow venting. The portal system was then accessed via inferior mesenteric vein for portal system flush. Cold preservation fluid, consisting of University of Wisconsin solution (UW), heparin, and glutathione, was used in all cases. After completion of the preservation solution infusion, the liver was then removed from abdomen, and the biliary system flushed on the back table. Finally, the liver was packaged in cold UW solution and transported back to the hospital for implantation. Thrombolytic agents were not used in either donor or recipient.

All transplants were performed utilizing the piggyback technique without either a porto-caval shunt or caval clamping. Duct-to-duct biliary reconstruction with transcystic biliary tube (5-Fr ureteral stent, Bard polyurethane ureteral catheter, C. R. Bard, Inc, Covington, GA, USA) was used except in recipients when deemed not feasible by the recipient surgeon [9]. In patients with primary sclerosing cholangitis, a choledochojejunostomy reconstruction with a transjejunal biliary tube was used. All patients with transcystic or transjejunal biliary tubes had cholangiogram on post-transplant day 3 and day 21 or when deemed clinically necessary. After a post-transplant cholangiogram on day 3, the biliary tube is capped until day 21 cholangiogram. If this cholangiogram reveals a normal biliary tree, the biliary tube is then removed.

Intrahepatic bile duct strictures (ITBS) was defined as diffuse, intrahepatic bile duct strictures, in the absence of HAT, diagnosed with either cholangiogram using an intraoperatively placed transcystic duct biliary tube, or by endoscopic retrograde cholangiopancreatogram (ERCP) or percutaneous transhepatic cholangiogram (PTC). All cholangiograms were reviewed retrospectively and post-LT day of ITBS diagnoses were recorded.

Statistical analysis

Comparison of variables between patient groups was performed, as appropriate, using *t*-test, Mann–Whitney *U*-test, and chi-square test. Time-to-graft loss, whether because of death or re-transplantion, was recorded. Cases were censored at the time of the end of the study or date of last correspondence for losses to follow-up. Kaplan–Meier method and log-rank test was used to estimate and examine patient and graft survival. Association between events during procurement and the development of ITBS and overall biliary complications were examined using logistic regression. In logistic regression analyses, variables significant at $P < 0.20$ on univariate analysis as well as variables that may have confounding effects or are of clinical importance were entered in the initial multivariate model. A P value of <0.05 was considered statistically significant. Statistical analysis was performed using SPSS 17.0 (Chicago, IL, USA).

Results

Between December 1998 and December 2010, a total of 215 LT were performed using DCD liver grafts at the Mayo Clinic Florida Transplant Program. The mean follow-up time was 49.8 months (median: 47.4; range 0–139 months).

Recipient and donor characteristics and peri-operative data are summarized in Table 1. Recipients were more likely to be male patient (73.5%), with a mean calculated MELD score of 17.7 ± 7.7 (range: 6–61); 12 patients (5.6%) were also recipients of kidney grafts at the time of LT; whereas 10 patients (4.7%) had prior LTs. DCD donors were more likely to be male patient; with mean age of 40.1 ± 16.2 (range: 7–81) years and from the local OPO (56.3%). Mean CIT was 6.0 ± 1.48 h (range: 3.4–10.8), whereas mean implantation WIT was 33.7 ± 12.2 min (range: 17–106).

Postoperative complications are shown in Table 2. Twenty-seven patients (12.6%) were diagnosed with ITBS. Of these, 12 recipients (44. 4%) were retransplanted, whereas seven patients (25.9%) died before receiving a second liver graft. The remaining eight patients (29.6%) (median age: 57.5; range: 39–72) are currently alive (median follow-up: 39 months; range: 23–61 months); these patients have had a complicated postoperative course: one patient required reoperation for postoperative hemorrhage; four patients experienced postoperative bacteremia; all eight patients underwent 1–3 ERCPs within the first postoperative year; however, none of these patients required any additional surgical or endoscopic/percutaneous treatment beyond the first post-transplant year. Overall, 18 patients were diagnosed with ITBS during the first month after LT, whereas the remaining patients were diagnosed between 1 and 6 months after LT. Twenty-seven patients who had ITBS also had other biliary complications: 16 (59.3%) patients had extrahepatic strictures, one (3.7%) patient had bile leak and four (14.8%) patients had both strictures and bile leak.

Extrahepatic biliary strictures and bile leak requiring surgical or percutaneous intervention were diagnosed in 31 additional recipients (14.4%): 12 patients (5.5%) had extrahepatic biliary stricture only; eight patients (3.7%)

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Table 1. Recipient, donor characteristics, and peri-operative values.

Recipient characteristics	
Recipient age (years)	55.26 ± 9.56 (15–75; 50, 55, 61)
Recipient sex, male	158 (73.5%)
Raw MELD	17.71 ± 7.75 (6–51; 12, 16, 21)
Recipient race	
Caucasian	199 (92.6%)
African-American	11 (5.1%)
Other	5 (2.4%)
Multi-organ transplant	12 (5.6%)
Prior liver transplant	10 (4.7%)
Donor characteristics	
Donor age (years)	40.11 ± 16.18 (7–81; 25, 41, 53)
Donor sex, males	150 (69.8%)
Donor weight (kg)	82.2 ± 21.23 (30–233; 70, 80, 91)
Donor height (cm)	173.14 ± 11.03 (167, 175, 180)
Donor BMI (kg/m^2)	27.45 ± 6.82 (13.4–71.9; 23.4, 26.5, 30.1)
Donor race	
Caucasian	191 (88.8%)
African-American	16 (7.4%)
Other	8 (3.8%)
DRI	1.96 ± 0.50 (1.54, 1.85, 2.27)
Share status	
Local	121 (56.3%)
National	17 (7.9%)
Regional	77 (35.8%)
Donor cause of death	
Anoxia	55 (25.6%)
CVD/stroke	50 (23.3%)
Head trauma	103 (47.9%)
Other	7 (3.3%)
Peri-operative values	
Pre-transplant INR	1.69 ± 0.77 (0.9–10; 1.3, 1.5, 1.9)
Pre-transplant Total Bilirubin (mg/dl)	5.26 ± 8.69 (0.2–62.7; 1.5, 2.6, 4.5)
Pre-transplant Creatinine (mg/dl)	1.16 ± 0.88 (0.3–7.4; 0.7, 0.9, 1.3)
Intra-operative pRBC transfusion (units)	3.60 ± 3.17 (0–21.7; 1.75, 2.8, 4.55)
Post-transplant peak ALT (u/l)	1082.76 ± 1087.73 (76–7632; 420, 653, 1351)
Post-transplant peak AST (u/l)	2490.71 ± 3368.41 (88–22800; 706, 1405, 2636)
Post-transplant trough factor 5 (%)	33.69 ± 17.40 (7–148; 23, 32, 42)
CIT (hours)	6.00 ± 1.48 (3.4–10.8; 1.98, 5.73, 6.73)
WIT (minutes)	33.69 ± 12.24 (17–106; 26, 32, 39)

Continuous variables in mean ± SD (min–max; 25th, 50th, 75th percentile) categorical variables in *n* (%).

had bile leak only; 11 patients (5.1%) had a combination of bile leak and extrahepatic biliary stricture. All anastomotic bile leaks ($n = 19$) were diagnosed within 21 days after LT (with cholangiogram either by transcystic biliary tube or by ERCP). Of 12 patients who had extrahepatic biliary stricture only, seven patients were diagnosed within 21 days after LT (with cholangiogram either by transcystic biliary tube or by ERCP); five patients were diagnosed between 1 and 9 months after LT (with cholangiogram either by ERCP or PTC).

Five patients (2.3%) had PNF and seven patients (3.3%) had HAT.

For the whole DCD group, mean DWIT was 25.3 ± 10.8 min (median: 24; range: 4–85); mean asystole-cross clamp period was 9.4 ± 3.2 min (median: 9; range: 3–21); mean incision-to-cross clamp period was 4.2 ± 2.2 min (median: 4; range: 1–12). Mandatory wait period after asystole was available in 189 cases: there was a 2-min wait time in 68 cases, whereas this was 5 min in 121 cases. The mean asystole-cross clamp period was 6.4 ± 0.4 min (median: 6; range: 3–12) for the 2-min mandatory wait group ($n = 68$); 10.3 ± 0.3 (median: 10; range: 7–21) for the 5-min mandatory wait group ($n = 121$), ($P = 0.001$). There was no information available regarding the location of the patient at the time of withdrawal of life support.

Specific time periods during DCD procurement in recipients who were diagnosed with ITBS versus no ITBS

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Table 2. Postoperative complications of DCD liver graft recipients [categorical variables in *n* (%)].

Postoperative complications	
Primary nonfunction	5 (2.3%)
Hepatic artery thrombosis	7 (3.3%)
Hepatic artery stenosis	11 (5.1%)
ITBS	27 (12.6%)
Extrahepatic biliary complications	52 (24.1%)
Leak	9 (4.2%)
Extrahepatic strictures	28 (13.0%)
Leak and extrahepatic stricture	15 (6.9%)
Re-operations (excluding re-transplants)	30 (14.0%)
Biliary	12 (5.6%)
Hemorrhage	18 (8.4%)
Graft loss	73 (33.9%)
Death	43 (20.0%)
Biliary complications	7 (3.3%)
Other	36 (16.7%)
Retransplant	30 (13.9%)
Biliary complications	12 (5.5%)
Other	18 (8.4%)

are illustrated in Table 3. Of all the time periods during procurement, only asystole-cross clamp period was significantly different between the two groups (10.65 ± 3.96 vs. 8.81 ± 3.27, $P = 0.048$). Differences in time periods in recipients who had no biliary complications versus recipients with overall biliary complications (includes ITBS and extrahepatic biliary complications) versus recipients with only extrahepatic complications are illustrated in Table 4: asystole-cross clamp period was significantly different between the recipients with no biliary complications versus recipients with overall biliary complications (8.73 ± 3.30 vs. 9.80 ± 3.59, $P = 0.047$). When recipients who had no biliary complications were compared to the recipients with extrahepatic biliary complications only, none of the variables achieved statistical significance.

Predictors for development of ITBS and overall biliary complications were examined using separate logistic regression analyses (Table 5). On multivariate analysis, only asystole-cross clamp duration was a significant predictor for development of ITBS (OR 1.160, 95% CI: 1.029–1.309, $P = 0.015$). Each minute increase in asystole-cross clamp duration was associated with a 16% increase in odds for development of ITBS. Similarly, asystole-cross clamp duration was predictor for development of overall biliary complications (OR 1.108, 95% CI: 1.010–1.214, $P = 0.029$).

We compared 2-min and 5-min wait periods for development of ITBS and overall biliary complications: there was tendency for more ITBS in the 5-min wait period group; however, this did not reach statistical significance (10.3% vs. 14.8%, $P = 0.40$). Similarly, there was a tendency for more overall biliary complications in 5-min mandatory period without reaching statistical significance (22.4% vs. 32.4%, $P = 0.16$).

Graft and patient survival

Graft survival for DCD group at 1, 3, and 5 years was 80.9%, 72.7%, and 69.1%. Patient survival for DCD group at 1, 3, and 5 years was 92.6%, 85.0%, and 76.7%.

Discussion

As the liver graft scarcity intensifies, an emphasis on expanding donor criteria occurs.

The widespread and successful utilization of DCD grafts could provide more timely access to LT. Systematic utilization of extended criteria donors, including DCD donors, maximizes donor use, increases access to LT, reduces wait list mortality by providing satisfactory outcomes in select recipients [12,13]. Most LT are performed with DBD organs. Advances in traumatology, neurosurgery, and neuroradiology have improved immediate survival after devastating brain injury. As a result, patients who are destined to become multiorgan donors are

Table 3. Comparison of procurement time points in DCD liver grafts with diagnosis of ITBS versus no ITBS (seven patients who had HAT and five patients who had PNFs were excluded from analysis).

	No ITBS	ITBS	*P*
DCD WIT	24.31 ± 8.70 (18, 24, 30)	24.41 ± 7.67 (19, 24, 30)	0.756
Withdrawal-asystole	15.36 ± 8.55 (10, 14, 19)	14.42 ± 6.07 (9.75, 13, 19)	0.819
Asystole-cross clamp	8.81 ± 3.27 (7, 8, 11)	10.65 ± 3.96 (8, 10, 12.25)	**0.048**
Hypotensive WIT			
Withdrawal-SBP < 50	10.24 ± 8.42 (5, 9, 14)	10.39 ± 56.8 (6, 10, 15)	0.405
SBP < 50-Asystole	5.2 ± 5.09 (1, 3, 8)	3.35 ± 4.59 (1, 3,5)	0.176
SBP<50-cross clamp	14.13 ± 5.84 (10, 13, 17)	14.26 ± 4.84 (11, 13, 17)	0.839
Hypoxic WIT			
Withdrawal-O2 Sat < 30	8.19 ± 7.03 (4, 6,11)	8.76 ± 5.71 (4, 7, 12.5)	0.483
O2 Sat < 30-asystole	7.51 ± 6.12 (3, 7, 11)	5.67 ± 4.28 (2, 4, 9.5)	0.305
O2 Sat < 30-cross clamp	16.52 ± 6.75 (11, 16, 21)	16.52 ± 5.29 (12, 16, 19.5)	0.998

Values in minutes, presented as mean ± SD (25th, 50th, 75th percentile).
Bold values indicates significant at $P < 0.05$.

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Table 4. Comparison of procurement time points in DCD grafts with no biliary complications versus with diagnosis of overall biliary complications (includes ITBS and extrahepatic biliary complications) and with diagnosis extrahepatic biliary complications in the absence of ITBS.

	No biliary complications	Overall biliary complications	*P**	Extrahepatic biliary complications (non-ITBS patients)	*P*‡
DWIT	24.79 ± 9.23 (18, 24, 31)	23.29 ± 6.74 (19, 22.5, 29)	0.252	22.43 ± 5.90 (18, 22, 26)	0.066
Withdrawal-asystole	15.79 ± 9.13 (9.75, 13, 18)	14.00 ± 5.77 (10, 13, 19)	0.110	13.73 ± 5.60 (10, 14, 20)	0.214
Asystole-cross clamp	8.73 ± 3.30 (7, 8, 11)	9.80 ± 3.59 (8, 10, 11)	**0.047**	9.12 ± 3.18 (6.5, 9, 10.5)	0.543
Hypotensive WIT					
Withdrawal-SBP < 50	10.88 ± 8.96 (5, 9, 15)	8.98 ± 5.58 (5, 8, 13)	0.109	7.78 ± 5.30 (4, 7, 11)	0.088
SBP < 50-asystole	4.97 ± 5.24 (1, 3, 8)	4.36 ± 4.23 (1, 4, 6)	0.474	5.22 ± 4.59 (2, 4, 8)	0.820
SBP < 50-cross clamp	14.04 ± 6.17 (10, 13, 17)	14.38 ± 4.56 (11, 13.5, 18.5)	0.728	14.48 ± 4.40 (11, 14, 18)	0.727
Hypoxic WIT					
Withdrawal-O2 Sat < 30	8.60 ± 7.60 (4, 6, 11)	7.54 ± 4.76 (4, 7, 11)	0.388	6.52 ± 3.61 (4, 6, 10)	0.187
O2 Sat < 30-asystole	7.78 ± 6.52 (2.75, 7, 11.25)	6.07 ± 4.12 (2.75, 6, 9.25)	0.532	6.40 ± 4.04 (3, 6, 10)	0.186
O2 Sat < 30-cross clamp	16.71 ± 7.22 (11, 16, 21.25)	16.09 ± 4.78 (12, 16, 19)	0.700	15.72 ± 4.38 (13, 16, 19)	0.382

Values in minutes, presented as mean ± SD (25th, 50th, 75th percentile).
Bold values indicates significant at $P < 0.05$.
*No biliary complications versus biliary complications.
‡No biliary complications versus non-ITBS Biliary complications.

Table 5. Single and multi variable analysis for the causes of ITBS and overall biliary complications (includes ITBS and extrahepatic biliary complications).

	Single variable		Multiple variable*	
	OR (95% CI)	*P*	OR (95% CI)	*P*
ITBS				
DCD WIT	0.994 (0.950–1.041)	0.806		
Asystole-cross clamp period	1.161 (1.028–1.311)	**0.016**	1.160 (1.029–1.309)	**0.015**
BP < 50-cross clamp period	0.993 (0.928–1.062)	0.837		
O2 Sat < 30-cross clamp period	0.989 (0.928–1.054)	0.730		
Overall biliary complications				
DCD WIT	0.982 (0.949–1.015)	0.284		
Asystole-cross clamp period	1.112 (1.015–1.219)	**0.022**	1.108 (1.010–1.214)	**0.029**
BP < 50-cross clamp period	0.995 (0.947–1.045)	0.841		
O2 Sat < 30-cross clamp period	0.976 (0.930–1.023)	0.312		

*Controlling for CIT and donor age.
Bold values indicates significant at $P < 0.05$.

increasingly not meeting cirteria for brain death [7]. Families wishing to donate in such circumstances can do so only after cardiac death occurs following discontinuation life support in intensive care. DCD grafts offer an opportunity to maintain, if not increase the number of LT performed. The widespread acceptance and utilization of DCD grafts has been constrained by lower graft survival and higher biliary complication rates than in DBD liver grafts [4,5]. If DCD is to become a reliable source of liver grafts, the underlying problems leading to ITBS and overall biliary complications must be recognized and solved. Ensuring excellent outcomes with such organs warrant refinement of the techniques for procurement. Our transplant program started using liver grafts from DCD donors in 1998. We previously reported on our experience with DCD grafts, demonstrating low ITBS and graft loss rates in comparison with other published single institution reports [9,14]. Most of the current practice recommendations, such as DWIT recommendations, come from early experience and interpretation of small data sets [10,15]. The purpose of the current report is to better characterize the events during DCD procurement in relation to development of ITBS and overall biliary complications.

Intrahepatic bile duct strictures (ITBS) is the leading cause for DCD graft loss. This complication has prevented the widespread acceptance of DCD graft use by transplant centers [6]. Even though the exact mechanism is not well-known, the combination of warm ischemia at the time of procurement and reperfusion in the recipient results in compromised blood flow in the peribiliary vasculature [16]. It is recognized that ischemic injury to graft occurs during and after organ recovery. This is perhaps increased in DCD donation when the warm ischemia time, when there is limited or no blood flow to the end-organs before perfusion of cold preservation fluid, occurs. The injury

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associated with warm ischemia is considered most deleterious, especially when it is prolonged [17]. ITBS is not reversible and management options after LT are limited. Identification of the factors playing a role in the development of ITBS and devising preventive strategies are crucial to encourage greater utilization of these grafts.

Donation after cardiac death donors (DCD donors) progress to death by going through agonal phase characterized by hemodynamic changes till asystole occurs. The agonal phase during procurement may have deleterious effect on liver grafts: the parenchymal damage incurred during significant hemodynamic changes may cause a nonfunctioning graft in the short-term and it may cause problems, such as ITBS and extrahepatic biliary complications in the long term. There has not been a previous formal report in the literature evaluating the link between the agonal phase during procurement and outcomes after DCD LT. In a small observational study, Ho *et al.* noted that the duration of SBP <50 mmHg to cold flush predicted poor graft survival in DCD LT with 38% of grafts reached a composite end-point of death, graft loss or ITBS within one year [18]. Similar to the findings in the current analysis, they found that DWIT was not predictive for poor outcome.

Organ specific delivery of blood and oxygen could be different for different organs [8]. Crude measurements, such as DWIT (encompassing the period between withdrawal of life support until infusion of cold preservation solution) may not be granular enough to characterize risks. DWIT encompasses not only the agonal phase, but also the mandatory wait period as well as the time spent from incision-to-cross clamp of aorta. Previously, the DWIT was thought to be a factor in development of ITBS; accordingly procurement protocols in single institutions limit DWIT to around 20–30 min and the American Society of Transplant Surgeons (ASTS) recommends minimization of DWIT [10,19]. In our analysis, DWIT was not a significant factor for the development of ITBS or overall biliary complications, which may be a function of the small overall variation in time. When we examined the individual time points after withdrawal of life support, asystole-cross clamp duration was a significant determinant of ITBS and overall biliary complication development. Asystole-cross clamp time includes the mandatory wait period and the period between incision and cross clamp. It is important to note that recommendations for mandatory wait time vary: the ASTS recommends a mandatory wait period of 2 min whereas the Institute of Medicine recommends 5 min [10,11].

Rhee *et al.* in a large animal model found that hepatic circulation ceased before circulatory arrest occurred [8]. They argue that basing declaration of death on electrical activity may cause additional ischemia time on the organs of interest and perhaps a broader investigation into whether these declaration criteria have an impact on outcome is warranted. In a previous study, 62% of hospitals in one OPO did address declaration of death as irreversible cessation of circulation without elaboration on the method of confirmation, whereas only 11% stated to use arterial line for declaration of death [20]. We agree with previous assessment that how cessation of circulation is defined and how the death is defined could play a significant impact on DCD donors and moreover, they affect graft survival and biliary complications in the recipient. Criteria for declaration of death using electrical activity may indeed be flawed [21]. Perhaps, blood pressure monitoring with arterial line could be mandated to help standardize practices during procurement. Pulseless electrical activity generates no circulation, therefore, may be inconsequential in a death determination. As there is need to determine exact timing of asystole to determine death, it is essential to prove mechanical asystole [21]. Our experience presented herein clearly demonstrates that nonperfusion state plays a major role in defining future biliary complications including the most feared intra-hepatic, diffuse biliary strictures, and hepatic necrosis. In multivariate analysis, we did not see a significant effect of agonal phase. Within reasonable DWIT, prolongation of asystole-cross clamp period correlated with development of both ITBS and extrahepatic bile leaks and strictures. A 5-min mandatory wait time may be on the conservative side and it could perhaps be reduced to 2 min as ASTS recommends. We acknowledge that practice standards are intentionally conservative to maintain public confidence in the accuracy of death determination by eliminating the possibility of false-positive diagnoses. Although a case for shortening mandatory wait time can be discussed, procurement technique in individual programs deserves introspection. All the procurements in our experience were performed by experienced transplants surgeons with the help of procurement personnel experienced in DCD procurement. A short incision-cross clamp period is a reflection of the procurement team's experience. The goal of the rapid procurement technique in DCD donors is to clear the blood from the peribiliary arterioles in a rapid manner. Therefore, aortic cross-clamp provides a definite point of achievement for procurement surgeon. After realization of the fact that prolongation of asystole-cross clamp period correlated with development of biliary problems in the graft, we have paid particular attention to this period. In fact, till the end of 2011, only one liver graft was lost because of ITBS in the last 50 LT using DCD grafts. Although accepting a liver graft is up to the particular recipient surgeon's decision, we are now hesitant to accept a graft with asystole-cross clamp period of more than 10 min. As a reflection of this evolution, in our practice, no DCD liver graft was lost since 2009.

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Another possibility of shortening the nonperfusion state would be to use a modified ECMO (extracorporeal support with intraaortic occlusion balloon to prevent blood flow to heart and brain) [22]. As DWIT within a narrow limit in our experience did not correlate with development of ITBS or extrahepatic biliary complications, an argument could be made to use ECMO with extension of DWIT criteria [23].

It should be noted that there is no perfect way of collecting data at the time of DCD organ procurement; however, observations and analyses in this study should redirect the focus on the procurement practice itself. Large single center analyses have the advantage of consistent and homogeneous donor and recipient selection as well as peri- and postoperative recipient management. Although this is the largest reported single center experience detailing procurement factors, the number of DCD recipients is relatively small to adjust for all the risk factors for ITBS and overall biliary complications. The limited number of patients may also have resulted in type 1 error and clinically silent complications may have resulted in type 2 error. The findings in our analyses should be confirmed in a larger cohort from multiple institutions using DCD liver grafts.

In conclusion, our analysis clearly establishes a link between the development of ITBS and overall biliary complications with asystole-cross clamp period. Furthermore, hemodynamic changes in the agonal period during DCD liver procurement did not emerge as risk factors. Shortening of the mandatory wait period by regulatory bodies and efforts by individual transplant programs to shorten incision-cross clamp period present as two potential areas of improvement. The results of the study also raise the possibility of utilizing asystole to cross-clamp time in place of or in conjunction with DWIT in determining viability or quality of liver grafts.

Authorship

CBT: designed study, analyzed data, performed research/study, wrote the manuscript. IGB: designed study, collected data, analyzed data, wrote the manuscript. DKP, LS and DLW: collected data, performed research/study. DJK and JHN: final approval of manuscript.

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