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Controlled DCD Liver Transplantation Is Not Associated With Increased Hyperfibrinolysis and Blood Loss After Graft Reperfusion

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Background. The specific effect of donation after circulatory death (DCD) liver grafts on fibrinolysis, blood loss, and transfusion requirements after graft reperfusion is not well known. The aim of this study was to determine whether transplantation of controlled DCD livers is associated with an elevated risk of hyperfibrinolysis, increased blood loss, and higher transfusion requirements upon graft reperfusion, compared with livers donated after brain death (DBD). **Methods.** A retrospective single-center analysis of all adult recipients of primary liver transplantation between 2000 and 2019 was performed (total cohort n = 628). Propensity score matching was used to balance baseline characteristics for DCD and DBD liver recipients (propensity score matching cohort n = 218). Intraoperative and postoperative hemostatic variables between DCD and DBD liver recipients were subsequently compared. Additionally, in vitro plasma analyses were performed to compare the intraoperative fibrinolytic state upon reperfusion. **Results.** No significant differences in median (interquartile range) postreperfusion blood loss (1.2 L [0.5–2.2] versus 1.3 L [0.6–2.2]; $P = 0.62$), red blood cell transfusion (2 units [0–4] versus 1.1 units [0–3]; $P = 0.21$), or fresh frozen plasma transfusion requirements (0 unit [0–2.2] versus 0 unit [0–0.9]; $P = 0.11$) were seen in DCD compared with DBD recipients, respectively. Furthermore, plasma fibrinolytic potential was similar in both groups. **Conclusions.** Transplantation of controlled DCD liver grafts does not result in higher intraoperative blood loss or more transfusion requirements, compared with DBD liver transplantation. In accordance with this, no evidence for increased hyperfibrinolysis upon reperfusion in DCD compared with DBD liver grafts was found.

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INTRODUCTION

Despite over 21 000 orthotopic liver transplantations (OLTs) performed worldwide in 2018 alone,[1] the availability of donor livers for transplantation struggles to meet the ever-growing demand. This results in a high mortality rate on the waitlist.[2] In an effort to expand the donor organ pool and thus lower waitlist mortality, extended criteria donor livers such as livers donated after circulatory death (DCD)

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are being increasingly used.[3,4] With improvements in donor management and graft preservation, surgical technique, and anesthesiological advances, appropriate use of DCD livers, with minimal additional risk factors, results in acceptable graft and patient survival rates. However, DCD liver recipients still face an increased risk of postoperative morbidity, mainly as a result of ischemia-reperfusion (I/R) injury.[5-7]

Restoration of blood flow and the reestablishment of oxygen supply following a period of ischemia to a donor liver often triggers a profound inflammatory response (reperfusion injury) during OLT.[8,9] One characteristic of I/R injury is the activation of fibrinolysis, which is primarily mediated by endothelial cell activation that is triggered by both direct and indirect I/R cytotoxic mechanisms. Hyperfibrinolysis occurring after graft reperfusion could result in (severe) hemorrhage and the need for transfusion of substantial amounts of red blood cell (RBC), fresh frozen plasma (FFP), and platelet concentrate.[10-15] Previous studies have shown that high intraoperative blood loss and transfusions of human blood products are frequently associated with a higher incidence of surgical reintervention.[16] Moreover, it has also been shown that transfusion of a total of ≥3 units of RBCs during liver transplantation is specifically associated with increased posttransplant morbidity.[17]

The extent of I/R injury in OLT is exacerbated by prolonged ischemia times that occur during donor demise, organ procurement, and preservation before transplantation. Given the inevitable additional warm ischemia attributable to the agonal and cardiac arrest phases that occur, several studies have suggested that DCD liver transplantation is associated with higher intraoperative and postoperative blood loss as well as increased transfusion rates in comparison with DBD liver transplantation.[18,19] However, this specific effect of DCD livers on intraoperative hemostasis after reperfusion has yet to be investigated in depth. With 50% of all current donor livers available for transplantation derived from controlled (Maastricht type III) DCD donors in the Netherlands, the primary objective of this study was to investigate and assess the specific effect of controlled DCD liver transplantation on intraoperative hemostatic dysfunction.

We hypothesize that as a result of the additional I/R injury DCD livers incur, controlled DCD liver transplantation is indeed associated with exacerbated postreperfusion hyperfibrinolysis, leading to higher postreperfusion blood loss and transfusion requirements compared with DBD liver transplantation.

MATERIALS AND METHODS

Study Design and Population

A retrospective analysis of an observational cohort study (www.trialregister.nl—Trial NL6334) of adult (age ≥18 y) patients who underwent a primary OLT between the January 1, 2000 and the June 20, 2019 was performed (n = 628). Split/reduced liver graft transplantations (n = 22), combined organ transplantations (n = 27), domino transplantations (n = 2), and donor livers that underwent machine perfusion before transplantation (n = 37) were excluded. To allow for fair and valid comparison between the two groups, this cohort subsequently underwent propensity score matching (PSM) analysis to minimize the differences between donor and recipient characteristics. One-to-one matching generated a final total cohort of 218 patients (n = 109 patients per group) for further analysis.

This study was approved by the Medical Ethical Committee of our institute (METc 2014/77) and adhered to the Declaration of Helsinki and the Declaration of Istanbul.[20]

Data Collection

Donor and recipient characteristics, as well as intraoperative data during the distinct phases of OLT were obtained from a prospectively maintained computer database. When necessary, digital patient files were reviewed for missing information. Missing data per variable ranged between 0% and 8% in the total cohort; however, there were no missing data in the matched cohort. Variables determined to be relevant predictors of blood loss and transfusion requirements in the postreperfusion phase were selected for our analyses based on clinical experience and after a review of the literature.

Surgical Technique and Anesthetic Management

Surgical techniques, anesthetic management, and the blood transfusion policy in our center have been described previously.[21,22] The transfusion policy in our center is characterized by a restrictive use of blood products. RBC transfusions were administered to maintain a hematocrit level between 0.25 and 0.30, and administration of FFP and platelets was never solely dictated by laboratory values or results from viscoelastic analyses (ie, thromboelastography [TEG] or rotational thromboelastography). These products were only given in the presence of excessive blood loss, which could not be controlled by standard surgical measures. Moreover, cell-saver blood is typically not used during OLT at this center.

Outcome Measures

The primary endpoints for this study were postreperfusion blood loss and RBC transfusion requirements. The secondary endpoints were postreperfusion FFP and platelet transfusions, administration of fibrinogen concentrate or tranexamic acid as well as incidence post-OLT hemorrhage occurring within the first 7 d after transplantation.

With respect to intraoperative blood loss and transfusion requirements, the following variables were assessed in 3 phases (1—preanhepatic, 2—anhepatic [collectively noted as prereperfusion], and 3—postreperfusion) of the transplantation procedure. Blood loss was measured through collection of all blood suctioned from the surgical field during the OLT procedure into measuring containers. All used surgical gauzes were wringed and the blood was added to the above-mentioned containers. The total blood lost during each phase was subsequently recorded. Similarly, the number of units of allogeneic RBCs (1 unit approximately 250 mL), units of FFP (1 unit approximately 300 mL), units of thrombocyte/platelet concentrates (1 unit approximately 150 mL obtained from 5 donors), and amounts of fibrinogen concentrate and tranexamic acid were recorded upon administration.

In Vitro Laboratory Analysis

To gain further insight into and compare the fibrinolytic state of recipients of livers from DCD and DBD donors

during the OLT procedure, blood samples routinely collected during 30 consecutive OLT procedures were analyzed.

Plasma samples were retrieved from 14 recipients of a DBD liver and 16 recipients of a DCD liver from which blood samples from all time points were available. Selection of this subcohort was random (and based solely on the availability of all plasma samples from all 4 time points). Important to note, all these liver transplant recipients included in this substudy analysis belonged to the propensity score–matched cohort. Donor, recipient, and surgical characteristics are presented as supplementary information (**Tables S1** and **S2, SDC,** http://links.lww.com/TP/C148). Plasma collected from a group of 15 healthy volunteers was used as control.

Sample Collection

Arterial blood was collected at 4 different time points during OLT (ie, 30 min after induction of anesthesia [baseline]; 30 min after the start of the anhepatic phase, which we define as the moment the recipient native liver is taken out of the patient; and 30 min after portal reperfusion and at the end of transplantation, after the abdomen was closed) in sodium citrated tubes. All samples were then centrifuged (2700 rpm for 10 min at 18°C) and plasma was collected, snap-frozen, and stored at −80°C until analysis. Regarding the control group, venous blood samples were collected in sodium citrated tubes and thereafter handled similarly to the arterial blood samples of the subcohort collected during OLT.

Perioperative Viscoelastic Testing

Viscoelastic testing is routinely performed during OLT at our center. For the 30 patients included in the in vitro analysis, TEG was the modality used. For this analysis, a computer-controlled analyzer (software Version 4.1, TEG 5000 Thrombelastograph Hemostasis Analyzers; Haemoscope Corporation, Niles, IL) was used. Sampling time points for TEG analysis were (1) 30 min after induction of anesthesia, (2) anhepatic (30 min after removal of the native liver), and (3) 30 min after portal vein reperfusion. The measured thromboelastographic variables were reaction time (r), kinetic time or clot formation time (k), angle (a), maximal amplitude (ma), and clot lysis measured 30 min after ma (Ly30).

Assessment of Fibrinolysis

Clot lysis time (CLT) was measured using a standard procedure in which lysis of a tissue factor–induced clot by exogenous tissue plasminogen activator (tPA) was studied by monitoring changes in turbidity during clot formation and subsequent lysis, as described in detail previously by our group.[23] Concentrations of tPA antigen, plasminogen activator inhibitor-1 (PAI-1) antigen, and plasmin-antiplasmin (PAP) complexes were measured using an IMUBIND tPA ELISA kit, (Sekisui, USA via Werfen, Breda, the Netherlands), Quantikine Human Serpin E1/PAI-1 ELISA kit (Duoset DY1786 R&D systems, Abingdon, United Kingdom), and TECHNOZYM PAP complex ELISA kit (Technoclone, Vienna, Austria), respectively. All ELISAs were performed according to the manufacturers' instructions. In addition, concentration of D-dimer in the perfusion fluid was measured using an automated latex enhanced immunoassay (D-dimer HS 500, ACL 300 TOP, Instrumentation Laboratory, Breda, the Netherlands).

Statistical Analysis

Continuous normally distributed variables are presented as means and SD, whereas non-normally distributed variables are presented as medians and interquartile range (IQR). Categorical variables are presented as total numbers and percentages. Independent groups were compared using 2-sample *t* testing or the Mann-Whitney U test, depending on the distributions of the continuous variables. Categorical variables were compared using the Fisher exact test or Pearson χ^2 test. A P value of <0.05 was considered to indicate statistical significance.

To account for the heterogeneity between the DBD and DCD liver recipient groups and to ensure a valid comparison, PSM was performed. A multivariate logistic regression model was performed and propensity scores were created. Patient groups were matched for donor age, donor body mass index, donor sex, donor intensive care unit admission duration, cause of donor death, grade of steatosis of liver graft, organ preservation fluid, recipient age and sex, recipient body mass index, lab-model for end-stage liver disease (MELD) score, most recent serum creatinine and bilirubin, most recent recipient international normalized ratio, indication for transplantation, and status on the waitlist. Patients were matched 1:1 using a nearest-neighbor matching algorithm that attempted to match patients from either group based on the closest propensity score, with a difference of <10% of the SD of the scores. Paired patients were then used for comparison analysis on the degree of intraoperative blood loss and transfusion requirements between DBD and DCD liver transplantation. Unpaired patients were not added to this analysis. All statistical analyses were performed using SPSS Version 25 for Windows (SPSS Inc., Chicago, IL). For PSM, Propensity Score Matching R (R Foundation for Statistical Computing, Vienna Austria, Version 3.3.0), SPSS Python Essentials plug-in (IBM Corp., Armonk, NY, Version 25), and SPSS plug-in PS Matching in SPSS (Version 3.04) were additionally used.

RESULTS

Donor and Recipient Characteristics

From the total of 540 adult primary liver transplantations included in this study, 121 liver grafts (22%) were obtained from controlled DCD donors (Maastricht category III). Donor organs were allocated according to national policy (ie, an available donor organ was offered to the sickest patient on the waitlist) based on MELD score. Baseline characteristics of this cohort are summarized in Table 1. DCD donors were significantly younger compared to DBD donors (mean ± SD: 45 ± 13 versus 50 ± 15 y, $P < 0.001$) and had higher disease risk index (DRI) scores (2.1 ± 0.4 versus 1.5 ± 0.5, $P < 0.001$). However, this may be explained by the fact that circulatory death donation is one of the criteria necessary for calculating the disease risk index (DRI) score. DCD liver recipients were slightly older, had lower lab-MELD scores, and were transplanted with high urgency less frequently (Table 1).

After 1:1 PSM (n = 109 per group), no differences were seen in the majority of donor and recipient baseline characteristics between the two groups (Table 2). The only 2 exceptions were the type of organ preservation fluid used

TABLE 1.

Donor-recipient demographics and surgical parameters in total cohort

Variables	Total (n = 540)	DBD (n = 419)	DCD (n = 121)	*P*
Donor characteristics				
Age (y)	49 ± 15	50 ± 15	45 ± 13	**<0.001**
% missing	0.3%	0.2%	0.8%	
BMI (kg/m^2)	25 ± 3	25 ± 4	25 ± 3	0.17
(% missing)	0.5%	0.5%	0.8%	
Sex				0.06
Male	294 (54%)	220 (52%)	74 (61%)	
Female	246 (46%)	199 (48%)	47 (39%)	
% missing	0%	0%	0%	
Duration of ICU admission (d)	1 (1–3)	1 (1–3)	2 (1–4)	0.09
% missing	0.9%	0.9%	0.8%	
Cause of donor death				**<0.01**
Trauma	126 (22%)	99 (24%)	28 (23%)	
Cerebrovascular accident	328 (62%)	268 (64%)	61 (51%)	
Anoxia	19 (4%)	12 (3%)	7 (19%)	
Other	61 (11%)	38 (9%)	23 (6%)	
% missing	1%	0.5%	1%	
Macrovesicular steatosis				0.93
None	348 (64%)	264 (63%)	84 (70%)	
Steatosis <30%	128 (25%)	101 (24%)	27 (22%)	
30%–60%	23 (4%)	18 (4.8%)	5 (4%)	
<60%	1 (0.2%)	1 (0.2%)	0 (0%)	
% missing	6.8%	8%	4%	
DRI[a]	1.7 ± 0.5	1.5 ± 0.5	2.1 ± 0.4	**<0.001**
% missing	0.9%	0.7%	1.6%	
Organ preservation fluid				**<0.01**
HTK	143 (27%)	96 (23%)	47 (39%)	
UW	376 (70%)	305 (73%)	71 (59%)	
IGL-1	3 (0.5%)	3 (0.7%)	0 (0%)	
% missing	2.5%	3.3%	2%	
Recipient characteristics				
Sex				0.23
Male	317 (59%)	242 (58%)	75 (62%)	
Female	223 (41%)	177 (42%)	46 (38%)	
% missing	0%	0%	0%	
Age (y)	50 ± 13	49 ± 13	53 ± 12	**0.01**
% missing	0%	0%	0%	
BMI (kg/m^2)	26 ± 5.0	26 ± 4.5	26 ± 5.0	0.30
% missing	0.5%	0.7%	0%	
MELD score (lab-MELD)	16 (10–23)	16 (11–24)	14 (8–20)	**<0.01**
% missing	0.4%	0.5%	0%	
Serum creatinine before OLT (μmol/L)[a]	89 (72–137)	90 (74–156)	88 (65–121)	**0.02**
% missing	0.9%	1.0%	0.8%	
Serum total bilirubin before OLT (μmol/L)[b]	52 (24–134)	54 (28–141)	41 (17–118)	**0.02**
% missing	0.2%	0%	0.8%	
INR before OLT	1.4 (1.2–1.8)	1.4 (1.2–1.8)	1.3 (1.2–1.7)	0.23
% missing	0.2%	0%	0.8%	
Indication for transplantation				**0.02**
Fulminant hepatic failure	47 (9%)	42 (10%)	5 (4%)	
Noncholestatic	175 (32%)	142 (34%)	33 (28%)	
Cholestatic	130 (24%)	101 (24%)	29 (24%)	
Metabolic	70 (13%)	54 (13%)	16 (13.2%)	
Malignant	14 (2.6%)	8 (2%)	6 (5%)	
Other	102 (19%)	70 (16.5%)	32 (26%)	
% missing	0.4%	0.5%	0%	

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TABLE 1. (Continued)

Variables	Total (n = 540)	DBD (n = 419)	DCD (n = 121)	P
Status on waitlist				**<0.01**
Elective	488 (90%)	371 (89%)	117 (97%)	
High urgency	52 (10%)	48 (11%)	4 (3%)	
% missing	0%	0%	0%	
Surgical variables				
WIT in donor (min)[c]	NA	NA	16 ± 5	
			6%	
CIT of donor liver (h:min)[d]	7:42 ± 1:54	7:46 ± 2:00	7:27 ± 1:25	**0.05**
% missing	1.5%	1.4%	1.6%	
WIT in recipient (min)[e]	43 ± 14	46 ± 14	44 ± 13	**0.02**
% missing	1.7%	1.7%	1.6%	

Normally distributed continuous variables are presented as mean ± SD. Nonnormally distributed continuous variables and categorical variables are presented as median (interquartile range) and frequency (valid percentage), respectively. *P* value of <0.05 was considered to indicate statistical significance.

[a]Normal <110 μmol/L, to convert the value for creatinine to mg/dL, divide by 88.4.

[b]Normal 0–17 μmol/L, to convert the value for bilirubin to mg/dL, divide by 17.1.

[c]Time from circulatory arrest to in situ cold flush of donor organ.

[d]Time from in situ flushing of the donor organ until the liver is removed from ice for implantation.

[e]Time from removal of liver from ice until reperfusion via portal vein, hepatic artery, or both.

BMI, body mass index; CIT, cold ischemia time; DBD, donation after brain death; DCD, donation after circulatory death; DRI, disease risk index; HTK, histidine-tryptophan-ketoglutarate; ICU, intensive care unit; IGL-1, Institut Georges Lopez-1; INR, international normalized ratio; MELD, model for end-stage liver disease; NA, not available; OLT, orthotopic liver transplantation; UW, University of Wisconsin; WIT, warm ischemia time.

and serum creatinine. The difference in creatinine levels can be explained by the fact that DBD liver recipients tend to be sicker than recipients of DCD donor livers. Because of standard preservation protocol in the previous era, more DCD livers were mainly preserved with histidine-tryptophan-ketoglutarate in comparison with DBD livers (40% versus 20%; $P < 0.01$) (Table 2).

Postreperfusion Blood Loss and Transfusion Requirements

In the matched cohort, no significant differences in median postreperfusion blood loss (DCD 1.2 L [IQR, 0.5–2.2] versus DBD 1.3 L [IQR, 0.6–2.2]; $P = 0.62$) and median RBC transfusions (DCD 2 units [IQR, 0–4] versus DBD 1.1 units [IQR, 0–3]; $P = 0.21$) were observed between the groups (Figure 1A and B). Similarly, there was no significant difference in postreperfusion FFP transfusion between the two groups, and with the exception of a few cases, postreperfusion platelet transfusions were generally not required for neither DBD nor DCD liver recipients (Table 3). Fibrinogen concentrate or tranexamic acid is seldom administered during OLT in our center. Unfortunately, collection of these data only began in 2010; therefore, data from 44% of matched cohort (n = 95) were analyzed. Fibrinogen concentrate or tranexamic acid were administered in 18 patients only (DBD: 10; DCD: 8). In this group, 95% received 1 g of fibrinogen and 100% received ≤500 mg of tranexamic acid postreperfusion. No difference in the amounts of fibrinogen and tranexamic acid administered between DCD and DBD was observed ($P = 0.73$, $P = 0.90$, respectively).

The incidence of (severe) postoperative hemorrhage within the first 7 d after transplantation in DCD liver recipients was similar to that of DBD liver recipients (Table 3).

In Vitro Laboratory Assessment of Fibrinolysis

In a subset of patients belonging to the matched cohort, we further investigated the intraoperative fibrinolytic profiles of patients undergoing OLT. Shortest CLTs were observed 30 min after reperfusion; median 49 min (IQR, 32–53) and median 52 min (IQR, 35–95) in recipients from DCD livers (n = 16) and DBD livers (n = 14), respectively ($P = 0.13$) (Figure 2A). At the end of the surgery, CLTs increased and some samples showed no lysis at all. The inhibition of clot lysis during this phase was associated with a transient increase in PAI-1 levels, resulting in the inhibition of clot lysis (Figure 2D). Nonetheless, CLT at all points during transplantation did not significantly differ between the two groups. No significant differences were seen in postreperfusion PAP complex, tPA, and PAI-1 antigen levels between DCD liver recipients and DBD liver recipients (Figure 2B–D).

D-Dimer levels increased following graft reperfusion in both groups; with significantly higher levels in DCD liver recipients. However, this difference was because of initially higher D-dimer levels observed at baseline. Baseline D-dimer levels in DCD liver recipients at the start of OLT were nearly 3-fold higher than in the DBD liver recipients (median [IQR], 4399 [1477–13248] versus 1653 [691–2016] ng/mL; $P = 0.03$) (Figure 2E). To correct for these baseline differences such that the sole effect of reperfusion could be investigated, we calculated increases in D-dimer levels at 30 min postreperfusion and at the end of OLT compared with baseline. Both groups exhibited slight increases in D-dimer levels postreperfusion compared with prereperfusion levels and a negligible increase in levels at the end of OLT compared with prereperfusion, with the DBD liver recipients having slightly greater increments. These differences, however, were not statistically significant ($P = 0.26$) (Figure 2F).

Thromboelastography

No differences in the speed of clot formation, clot strength, and subsequent clot lysis between DCD and DBD liver recipients of this subcohort were observed at all 3 sampling points during OLT (Table 4). Moreover, both groups exhibited normal CLTs throughout the surgery.

TABLE 2.

Donor-recipient demographics and surgical parameters in propensity score–matched cohort

Variables	Total (n = 218)	DBD (n = 109)	DCD (n = 109)	*P*
Donor characteristics				
Age (y)	46 ± 14.6	48 ± 15.6	45 ± 13.5	0.17
% missing	0%	0%	0%	
BMI (kg/m^2	25 ± 4	25 ± 5	25 ± 3	0.56
% missing	0.5%	0.5%	0%	
Sex				0.11
Male	124 (57%)	57 (52%)	67 (62%)	
Female	94 (43%)	52 (48%)	42 (38%)	
% missing	0%	0%	0%	
Duration of ICU admission (d)	1 (1–3)	1 (1–3)	2 (1–4)	0.32
% missing	0.0%	0.0%	0.0%	
Cause of donor death				0.30
Trauma	53 (24%)	26 (24%)	27 (25%)	
Cerebrovascular accident	122 (56%)	67 (61%)	55 (51%)	
Anoxia	9 (4%)	3 (3%)	6 (5%)	
Other	33 (15%)	13 (12%)	20 (19%)	
% missing	1%	0%	1%	
Macrovesicular steatosis				
None	153 (70%)	74 (68%)	79 (73%)	
Steatosis <30%	56 (26%)	31 (28%)	25 (23%)	0.68
30%–60%	9 (4%)	4 (4%)	5 (4%)	
<60%	0 (0%)	0 (0%)	0 (0%)	
% missing	0%	0%	0%	
DRI[a]	1.8 ± 0.6	1.6 ± 0.6	2.1 ± 0.4	**<0.001**
% missing	0%	0%	0%	
Organ preservation fluid				**<0.01**
HTK	66 (30%)	22 (20%)	44 (40%)	
UW	152 (70%)	87 (80%)	65 (60%)	
IGL-1	0 (0%)	0 (0.6%)	0 (0%)	
% missing	0%	0%	0%	
Recipient characteristics				
Sex				0.50
Male	133 (61%)	67 (62%)	66 (60%)	
Female	85 (39%)	42 (38%)	43 (40%)	
% missing	0%	0%	0%	
Age (y)	54 (47–60)	54 (47–58)	54 (46–61)	0.32
% missing	0%	0%	0%	
BMI (kg/m^2)	26 ± 4.7	26 ± 4.0	26 ± 5.0	0.64
% missing	0%	0%	0%	
MELD score (lab-MELD)	16 ± 9	17 ± 9	15 ± 10	0.16
% missing	0%	0%	0%	
Serum creatinine before OLT (μmol/L)[a]	88 (72–124)	90 (77–133)	88 (65–116)	**0.03**
% missing	0%	0%	0%	
Serum total bilirubin before OLT (μmol/L)[b]	42 (20–100)	45 (25–106)	40 (17–84)	0.17
% missing)	0%	0%	0%	
INR before OLT	1.3 (1.2–1.7)	1.3 (1.2–1.6)	1.3 (1.2–1.7)	0.75
% missing	0%	0%	0%	
Indication for transplantation				0.11
Fulminant hepatic failure	13 (6%)	9 (8%)	4 (4%)	
Noncholestatic	72 (33%)	43 (39%)	29 (26%)	
Cholestatic	47 (22%)	22 (20%)	25 (23%)	
Metabolic	29 (13%)	14 (13%)	15 (14%)	
Malignant	9 (4%)	2 (3%)	6 (6%)	
Other	48 (22%)	19 (17%)	30 (27%)	
% missing	0%	0%	0%	

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TABLE 2. (Continued)

Variables	Total (n = 218)	DBD (n = 109)	DCD (n = 109)	P
Status on waitlist				0.06
Elective	203 (93%)	98 (90%)	105 (97%)	
High urgency	15 (7%)	11 (10%)	4 (3%)	
% missing	0%	0%	0%	
Surgical variables				
WIT in donor (min)[c]	N/A	N/A	16 ± 5	
			7%	
CIT of donor liver (h:min)[d]	7:33 ± 1:52	7:37 ± 2:13	7:30 ± 1:26	0.62
(% missing)	0%	0%	0%	
WIT in recipient (min)[e]	44 ± 13	45 ± 12	43 ± 14	0.18
(% missing)	0%	0%	0%	

Normally distributed continuous variables are presented as mean ± SD. Non-normally distributed continuous variables and categorical variables are presented as median (interquartile range) and frequency (valid percentage), respectively. *P* value of <0.05 was considered to indicate statistical significance.
[a]Normal <110 μmol/L, to convert the value for creatinine to mg/dL, divide by 88.4.
[b]Normal 0–17 μmol/L, to convert the value for bilirubin to mg/dL, divide by 17.1.
[c]Time from circulatory arrest to in situ cold flush of donor organ.
[d]Time from in situ flushing of the donor organ until the liver is removed from ice for implantation.
[e]Time from removal of liver from ice until reperfusion via portal vein, hepatic artery or both.
BMI, body mass index; CIT, cold ischemia time; DBD, donation after brain death; DCD, donation after circulatory death; DRI, disease risk index; HTK, histidine-tryptophan-ketoglutarate; ICU, intensive care unit; IGL-1, Institut Georges Lopez-1; INR, international normalized ratio; MELD, model for end-stage liver disease; N/A, not available; OLT, orthotopic liver transplantation; UW, University of Wisconsin; WIT, warm ischemia time.

Most importantly, no differences in postreperfusion TEG parameters between DCD liver recipients and DBD liver recipients were seen.

DISCUSSION

Our findings demonstrate that controlled DCD liver transplantation is not associated with greater postreperfusion blood loss and transfusion requirements when compared with transplantation with DBD liver grafts. Moreover, recipients of DCD livers do not exhibit an increased hyperfibrinolytic profile after reperfusion nor do they face an increased risk of (severe) postoperative hemorrhage.

A generally accepted consensus on the specific effect of DCD liver transplantation on blood loss, transfusion requirements, and the incidence of the development of postoperative bleeding complications remains to be reached. In reference to recently published literature, our results dispute the findings and conclusions of a study by the London group in which DCD livers (Maastricht category III) were more likely to develop aggressive fibrinolysis upon reperfusion evidenced by significantly higher fibrinolytic markers on TEG upon reperfusion. This accordingly resulted in higher blood loss and increased transfusion rates as compared to DBD livers.[25] Similarly, the Barcelona group (in which uncontrolled DCD as opposed to controlled DCD liver transplantation is more commonly performed) reports greater postreperfusion hemodynamic instability resulting in higher blood loss and transfusion requirements to DCD liver grafts compared to DBD livers.[26] Blasi et al also describe a hypocoagulative profile in DCD liver recipients with longer clot formation times and weaker clot formation in the DCD group compared with DBD. Interestingly, neither of these phenomena were observed in our study. A likely explanation for this difference is the significantly longer donor warm ischemia times associated with uncontrolled DCD donation that influences the marginality of these grafts.

In line with the results described by the London group, a more recent study performed in North America reports profound hyperfibrinolysis, higher postreperfusion blood

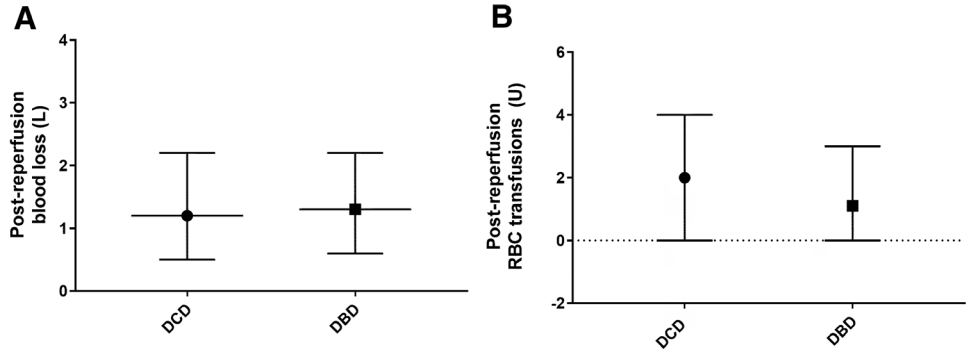

FIGURE 1. Scatter plots showing postreperfusion blood loss and RBC transfusion in DCD liver recipients compared with DBD liver recipients. A, Postreperfusion blood loss (L); (B) number of RBC units transfused postreperfusion. Graphs represent median values (error bars represent interquartile range). DBD, donation after brain death; DCD, donation after circulatory death; RBC, red blood cell.

TABLE 3.

Blood loss and transfusion requirements in propensity score–matched cohort

Variables	Total (n = 218)	DBD (n = 109)	DCD (n = 109)	P
Estimated blood loss prereperfusion (L)	1.4 (0.8–3.0)	1.3 (0.6–2.8)	1.4 (0.8–3.0)	0.30
% missing	8%	8%	8%	
Estimated blood loss postreperfusion (L)	1.2 (0.5–2.2)	1.3 (0.6–2.2)	1.2 (0.5–2.2)	0.62
% missing	6%	8%	6%	
Estimated total blood loss (L)	2.9 (1.7–5.5)	2.5 (1.6–5.0)	3.1 (1.9–5.7)	0.34
% missing	4%	2%	4%	
RBC transfusion prereperfusion (U)	1 (0–4.0)	0 (0–4)	1 (0–4.4)	0.45
% missing	4%	3%	4%	
RBC transfusion postreperfusion (U)	1.1 (0–3.3)	1.1 (0–3)	2 (0–4)	0.21
% missing	3%	3%	3%	
Total RBC transfusion (U)	3 (0–7)	3 (0–6)	3.3 (0–7.8)	0.41
% missing	2%	1%	2%	
FFP transfusion phase prereperfusion (U)	0 (0–1.5)	0 (0–1.5)	0 (0–1.6)	0.96
% missing	4%	3%	6%	
FFP transfusion postreperfusion (U)	0 (0–1.5)	0 (0–0.9)	0 (0–2.2)	0.11
% missing	2%	2%	4%	
Total FFP transfusion (U)	0 (0–3.9)	0 (0–3)	0 (0–4)	0.51
% missing	3%	2%	3%	
Platelet transfusion prereperfusion (U)	0 (0–0)	0 (0–0)	0 (0–0)	0.91
% missing	4%	2%	6%	
Platelet transfusion postreperfusion (U)	0 (0–0)	0 (0–0)	0 (0–0)	0.10
% missing	4%	2%	4%	
Total platelet transfusion (U)	0 (0–0)	0 (0–0)	0 (0–0)	0.39
% missing	4%	2%	4%	
Post-OLT bleeding complications				
7-d post-OLT hemorrhage				0.26
None	189 (86%)	97 (88%)	92 (85%)	
(Severe) bleeding requiring laparotomy	17 (8%)	8 (8%)	9 (8%)	
(Severe) bleeding not requiring laparotomy	12 (6%)	4 (4%)	8 (7%)	
% missing	0%	0%	0%	

Continuous variables are presented as median (interquartile range) and categorical variables as frequency (valid percentage). *P* value of <0.05 was considered to indicate statistical significance. DBD, donation after brain death; DCD, donation after circulatory death; FFP, fresh frozen plasma; OLT, orthotopic liver transplantation; RBC, red blood cell.

loss, higher transfusion requirements, and a higher incidence of postreperfusion hemodynamic instability in DCD liver transplantation as compared to DBD liver transplantation.[27] Contrastingly, a single-center retrospective study by the group in Rotterdam describes similar transfusion requirements and a comparable incidence of the development of postoperative vascular complications in DCD and DBD liver recipients.[24] The contradictory findings of these studies together highlight the difficulty in verifying the specific effect of DCD transplantation on intraoperative and postoperative hemostasis in liver transplantation. We believe that these differences may potentially be attributable to factors such as the variation in selection criteria of donor organs among different transplant centers and the variation in cold and warm ischemia times of the grafts before implantation. Moreover, the administration of ante mortem heparin in the donor, the difference in preservation fluids used during cold storage of the donor liver, or the administration of tissue plasminogen activator or other fibrinolytic agents into the liver allograft during implantation may influence intraoperative hemostasis.

To gain more insight from our results, we went further to investigate whether our clinical findings matched what occurred at biochemical level in plasma collected during the transplant procedures. We were able to conclude that DCD liver recipients do not exhibit significantly increased (hyper-) fibrinolytic profiles after reperfusion in comparison to DBD livers. This was evidenced by similar CLTs, absence of a significant release of D-dimer, PAP complexes, and plasma tPA antigen levels upon reperfusion in DCD liver recipients as compared to DBD liver recipients. Moreover, DCD liver recipients did not exhibit an increased hypocoagulative or hyperfibrinolytic profile on TEG following reperfusion when compared with DBD liver recipients.

This study is, to our knowledge, the first to primarily assess and compare bleeding risk and development of postoperative hemorrhage while simultaneously incorporating analysis of hyperfibrinolysis at biochemical level in DBD and DCD liver recipients. Our findings convincingly demonstrate that controlled DCD liver transplantation is not a particular risk factor for increased postreperfusion hyperfibrinolysis and consequently provides no increased risk of high intraoperative blood loss or greater transfusion requirements, compared with DBD liver transplantation. These findings may be because of the ongoing universal practice to ensure the minimization of procurement and

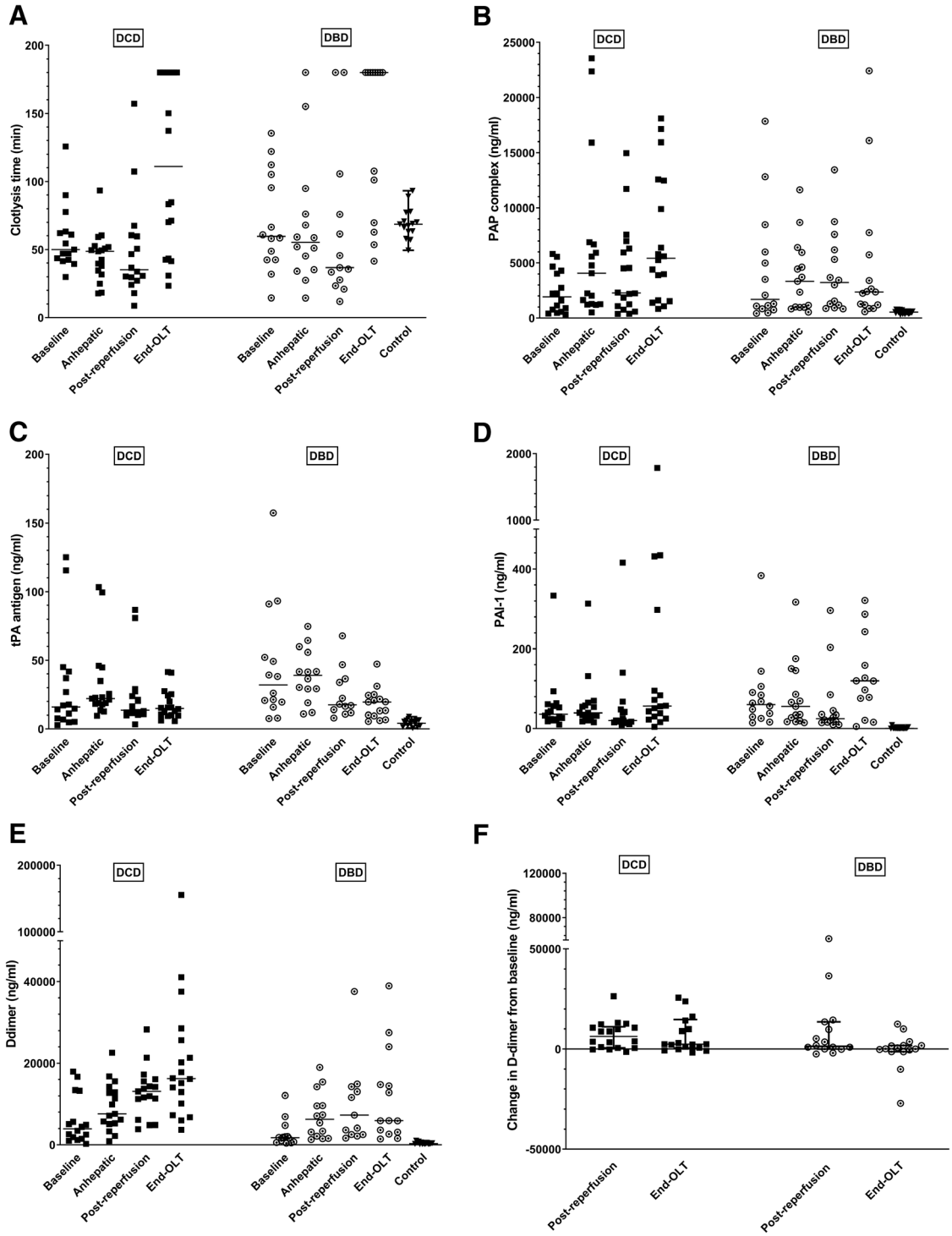

FIGURE 2. Comparison in the changes of levels of fibrinolysis markers in plasma between DCD and DBD liver recipients during transplantation: (A) Clot lysis time (min); (B) PAP complex (ng/mL); (C) tPA antigen (ng/mL); (D) plasminogen activator inhibitor-1 (PAI-1) antigen (ng/mL); (E) D-dimer (ng/mL); (F) change in D-dimer level from baseline (ng/mL). For all markers, plasma samples from healthy volunteers (n = 15) were used as controls. DBD, donation after brain death; DCD, donation after circulatory death; OLT, orthotopic liver transplantation; PAP, plasmin-antiplasmin; tPA, tissue plasminogen activator.

implantation times to limit ischemia and thus reduce the risk of I/R injury. Moreover, careful selection of suitable (extended criteria donor) donor organs (ie, limitation of the use of heavily steatotic livers or livers from uncontrolled DCD donors with long warm ischemic periods) as well as the careful selection of recipients who are capable of tolerating the particular physiological insult of end-ischemic reperfusion of a DCD organ is key. To ensure favorable outcomes after DCD liver transplantation at our center, DCD liver transplantations are typically performed in relatively younger patients undergoing a primary OLT.

We acknowledge that this study bears some limitations. The retrospective nature of the study suggests that definite conclusions from our results cannot be drawn with absolute certainty. Additionally, given the lack of collected data on postreperfusion syndrome, we were not able to

TABLE 4.

Perioperative TEG data from subcohort

TEG	DCD (n = 16)	DBD (n = 14)	*P*
Preanhepatic phase: 30 min after anesthesia induction			
R time (min)	19.8 (13.4–28.2)	17.4 (13.3–23.1)	0.60
K value (min)	9.4 (5.9–15.6)	6.2 (3.7–12.1)	0.31
α (°)	19.1 (13.5–32.2)	35.3 (20.2–46.8)	0.06
MA (mm)	45.2 (31.2–55.4)	56.3 (44.5–72)	0.53
LY 30 (%)	0.7 (0.1–1.6)	0 (0–0)	**0.01**
Anhepatic phase: 30 min after removal of native liver			
R time (min)	14.8 (11.5–19.7)	14 (8.9–19.1)	0.56
K value (min)	6.6 (4.7–10.7)	4.8 (4.0–6.6)	0.12
α (°)	29.9 (18.6–40.3)	42 (33–47.4)	**0.04**
MA (mm)	41.5 (35.1–54.4)	53.7 (40–58.5)	0.19
LY 30 (%)	0 (0.0–0.6)	0 (0–1.6)	0.50
Postreperfusion: 30 min after portal reperfusion			
R time (min)	19.2 (0–27.8)	26.6 (13–35.6)	0.34
K value (min)	9.1 (0–16.5)	14.6 (7.4–16.8)	0.31
α (°)	13.7 (0–19.9)	16 (9.8–28.7)	0.29
MA (mm)	25 (0–42.9)	42.7 (23.6–59.1)	0.06
LY 30 (%)	0 (0–0.5)	0 (0–0)	0.54

Data are presented as median (interquartile range). *P* values <0.05 are considered statistically significant.

Physiological reference range in pooled plasma: R time: 5–10 min, K value: 1–3 min, Alpha (α): 53°–72°, MA: 50–70 mm, Ly 30%: 0%–8%.[24]

α, rate of clot formation; DBD, donation after brain death; DCD, donation after circulatory death; K time, coagulation time to 20-mm clot; LY 30 (%), % of clot lysis at 30 min; MA, maximum amplitude (maximum strength of clot); R time, reaction time (time to fibrin formation 2-mm clot); TEG, thromboelastography.

investigate this phenomenon and compare the two groups. However, this study was still capable of achieving its aim of which intraoperative blood loss and transfusion requirements were the principal focus. Despite a relatively large cohort, these results are based on data collected at a single center. Therefore, the sample size and heterogeneity of the study population are limited.

Future studies prospectively assessing intraoperative hemostatic data collected from multiple centers, perhaps also involving data from numerous countries, are necessary to investigate this further to ensure that a reliable, widely extrapolated consensus can be reached. Nevertheless, this study shows that the use of controlled DCD livers poses no increased risk of postreperfusion bleeding, increased transfusion requirements, and development of severe postoperative hemorrhage in primary OLT. These findings are encouraging as they emphasize the safety of the utilization of controlled DCD livers that are beneficial in boosting the pool of donor organs to help tackle the high demand.

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