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ORIGINAL ARTICLE

Retrospective Study

Donor preoperative oxygen delivery and post-extubation hypoxia impact donation after circulatory death hypoxic cholangiopathy

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Abstract

AIM: To evaluate donation after circulatory death (DCD) orthotopic liver transplant outcomes [hypoxic cholangiopathy (HC) and patient/graft survival] and donor risk-conditions.

METHODS: From 2003-2013, 45 DCD donor transplants were performed. Predonation physiologic data from UNOS DonorNet included preoperative systolic and diastolic blood pressure, heart rate, pH, SpO_2, PaO_2, FiO_2, and hemoglobin. Mean arterial blood

pressure was computed from the systolic and diastolic blood pressures. Donor preoperative arterial O_2 content was computed as [hemoglobin (gm/dL) × 1.37 (mL O_2/gm) × SpO_2%) + (0.003 × PaO_2)]. The amount of preoperative donor red blood cell transfusions given and vasopressor use during the intensive care unit stay were documented. Donors who were transfused ⩾ 1 unit of red-cells or received ⩾ 2 vasopressors in the preoperative period were categorized as the red-cell/multi-pressor group. Following withdrawal of life support, donor ischemia time was computed as the number-of-minutes from onset of diastolic blood pressure < 60 mmHg until aortic cross clamping. Donor hypoxemia time was the number-of-minutes from onset of pulse oximetry < 80% until clamping. Donor hypoxia score was (ischemia time + hypoxemia time) ÷ donor preoperative hemoglobin.

RESULTS: The 1, 3, and 5 year graft and patient survival rates were 83%, 77%, 60%; and 92%, 84%, and 72%, respectively. HC occurred in 49% with 16% requiring retransplant. HC occurred in donors with increased age (33.0 ± 10.6 years *vs* 25.6 ± 8.4 years, P = 0.014), less preoperative multiple vasopressors or red-cell transfusion (9.5% *vs* 54.6%, P = 0.002), lower preoperative hemoglobin (10.7 ± 2.2 gm/dL *vs* 12.3 ± 2.1 gm/dL, P = 0.017), lower preoperative arterial oxygen content (14.8 ± 2.8 mL O_2/100 mL blood *vs* 16.8 ± 3.3 mL O_2/100 mL blood, P = 0.049), greater hypoxia score >2.0 (69.6% *vs* 25.0%, P = 0.006), and increased preoperative mean arterial pressure (92.7 ± 16.2 mmHg *vs* 83.8 ± 18.5 mmHg, P = 0.10). HC was independently associated with age, multi-pressor/red-cell transfusion status, arterial oxygen content, hypoxia score, and mean arterial pressure (r^2 = 0.6197). The transplantation rate was greater for the later period with more liberal donor selection [era 2 (7.1/year)], compared to our early experience [era 1 (2.5/year)]. HC occurred in 63.0% during era 2 and in 29.4% during era 1 (P = 0.03). Era 2 donors had longer times for extubation-to-asystole (14.4 ± 4.7 m *vs* 9.3 ± 4.5 m, P = 0.001), ischemia (13.9 ± 5.9 m *vs* 9.7 ± 5.6 m, P = 0.03), and hypoxemia (16.0 ± 5.1 m *vs* 11.1 ± 6.7 m, P = 0.013) and a higher hypoxia score > 2.0 rate (73.1% *vs* 28.6%, P = 0.006).

CONCLUSION: Easily measured donor indices, including a hypoxia score, provide an objective measure of DCD liver transplantation risk for recipient HC. Donor selection criteria influence HC rates.

Key words: Orthotopic liver transplantation; Ischemic cholangiopathy; Hypoxic cholangiopathy; Donation after circulatory death; Biliary complications; Reperfusion injury

Core tip: Cholangiopathy is a common and devastating clinical complication developing in recipients following donation after circulatory death liver transplantation. Numerous published investigations have attempted to link the hemodynamic instability and hypoxemia following withdrawal of life support to the development of cholangiopathy, without success. Our research indicates that cholangiopathy is linked to the magnitude of hypoxemic, ischemic, and anemic hypoxia transpiring after life support withdrawal and can be represented by a donor hypoxia score. We recommend that the historically utilized nomenclature of ischemic cholangiopathy be replaced using a more physiologic-based and expansive term, hypoxic cholangiopathy.

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INTRODUCTION

Orthotopic liver transplantation remains the gold standard for patients with end stage liver disease. The critical shortage of brain-dead organ donors has increased the utilization of donation after circulatory death (DCD) liver grafts. Many studies have compared donation after brain death to DCD liver transplants and have noted either inferior[1-3] or comparable[4,5] graft survival and biliary complications in the DCD group[5-8]. Brain-dead donors, unlike DCD donors, do not experience an agonal phase where hepatobiliary hypoxia accrues. Taner *et al*[5] stated that events during DCD procurement, such as variations in hemodynamics, a mandatory wait period, or time from incision to cross clamp, all included in the donor warm ischemic time, may impact the outcome of DCD liver transplants. The relative contribution of these factors on donor graft and recipient outcome is unknown.

The primary purpose of our study was to assess the effect of DCD donor risk conditions (age, hemodynamics prior to and after extubation, the use of vasopressors or red blood cell transfusions, pre-operative hemoglobin, and pre-operative oxygen delivery) on development of hypoxic cholangiopathy (HC). Our secondary aim was to evaluate the different eras of donors to see if these factors were predictive of recipient HC.

MATERIALS AND METHODS

Approval for the study was obtained from the Colorado Multiple Institutional Review Board. Informed consent

was waived, because this was a retrospective analysis. We reviewed information pertaining to DCD from the University of Colorado database between 2003 and 2013. Recorded data included age, date of transplant, model for end-stage liver disease (MELD) score, and whether the patient had a complication from their transplant. Using the UNOS DonorNet, the donor ID and match ID for each donor and recipient were confirmed.

Outcome conditions

Outcomes were defined as graft and patient survival, the development of recipient HC in the graft, and the need for re-transplant. Patient survival, graft survival, and the need for re-transplant were obtained from the University of Colorado Database. HC was defined as common bile duct with intrahepatic duct strictures requiring stent dependence or common bile duct and intrahepatic duct necrosis. HC was diagnosed by endoscopic retrograde cholangiopancreatogram (ERCP) or percutaneous transhepatic cholangiogram (if ERCP was performed with inability to traverse roux limb), and simple anastomotic strictures were excluded from the analysis. We believe HC is a more accurate term for DCD livers, compared to ischemic cholangiopathy which implies that the hepatobiliary insult is limited to decreased hepatic vascular perfusion. Donor and recipient variables were evaluated as potential risk factors for the development of HC. Era 1 donors were defined as those from February 2003 to November 2009 and era 2 donors were defined as those from December 2009 to September 2013. A cut-off point was created for era 1 and era 2 donors, because a more liberal donor selection criterion was used for era 2 donors. One recipient was excluded from the HC analysis due to an intraoperative death.

Donor preoperative O_2 delivery risk conditions

Predonation physiologic data from UNOS DonorNet included initial and preoperative systolic blood pressure (BP), diastolic BP, heart rate, pH, SpO_2, PaO_2, FiO_2, and positive end-expiratory pressure (PEEP) level in cm H_2O. Mean arterial BP (MAP) was computed from the systolic BP and diastolic BP. Donor preoperative arterial O_2 content was computed as (hemoglobin × 1.37 × SpO_2) + (0.003 × PaO_2). P/F O_2 was computed as PaO_2 ÷ (FiO_2% × 0.01). UNOS DonorNet provided the amount of donor red blood cell (RBC) transfusions given during hospital admission, vasopressor administration, duration of cardiac arrest prior to arriving at the hospital, pre-procurement length of stay, and pre-extubation hemoglobin. Patients who were transfused $\geqslant$ 1 unit of RBC during preoperative hospitalization were categorized as the RBC group. Donor vasopressor administration prior to the withdrawal of support was categorized as none, 1, or $\geqslant$ 2. Patients who received $\geqslant$ 2 vasopressors in the preoperative period were classified as the multi-pressor group. Patients in either the RBC or multi-pressor group were denoted as the RBC/multi-pressor group.

Donor post-extubation risk conditions

Operating room donor hemodynamic variables were taken from the local organ procurement organization (OPO) DCD operating room (OR) flowsheet. Vital signs were calculated every one-to-five minutes following extubation and then every minute at the start of the agonal phase (systolic BP < 60 mmHg or SpO_2 < 80%) per OPO protocol. Donor BP was recorded using either an arterial cannula or a blood pressure cuff in 1 min intervals. SpO_2 was monitored using either a finger or ear probe, per the OPO policy. The donor OR variables included: age, diagnosis prior to procurement, time diastolic BP < 60 mmHg, time SpO_2 < 80%, time from extubation-to-asystole, time from extubation-to-aortic cross clamping, and time from asystole-to-aortic cross clamping. Using UNOS DonorNet, the following data were also obtained for analysis: the body mass index, amount of RBC given during the hospital admission, preoperative vasopressor administration stopped at the time of extubation, duration of cardiac arrest prior to arriving at the hospital, and pre-donation length of stay. Donor hypoxia accrual time was defined as the period from the onset of extubation-to-aortic cross clamping. Donor ischemia time was defined as the elapsed number of minutes from the onset of diastolic BP < 60 mmHg until aortic cross clamping. Donor hypoxemia time was defined as the elapsed number of minutes from the onset of SpO_2 < 80% until aortic cross clamping. Donor hypoxia score was defined as (donor ischemia time + donor hypoxemia time) ÷ preoperative hemoglobin.

Recipient risk conditions

Recipient variables were: the cause of cirrhosis (hepatitis C, Laennec's, alpha-1 antitrypsin, hepatitis B, hepatocellular carcinoma, nonalcoholic steatohepatitis, autoimmune, or cholangiocarcinoma), MELD score, cold ischemic time, warm ischemic time, and type of biliary anastomosis. Duct-to-duct anastomosis was used with or without transcystic biliary tubes. When a DCD liver was used for a retransplant, a Roux-en-Y choledochojejunostomy was performed (4 DCD livers were used for re-transplant). Cold ischemic time was defined as the time of cross clamp to out of ice. Warm ischemic time was the time out of ice to reperfusion of the hepatic veins and portal vein. The University of Colorado Transplant team abandoned venovenous in 1995. Therefore, all recipient liver transplants during this time period were performed off bypass.

DCD procurement process

All DCD donors were classified as Maastricht type 3[9]. The DCD livers were procured by one organ surgical specialist provided by our local organ procurement

Table 1 Donor risk conditions for hypoxic cholangiopathy

	Result	Range
Age	29.7 ± 10.4	9-53
Body mass index (kg/m^2)	25.7 ± 4.1	18-36
Pre-op pressors = 0	29/44 (65.9%)	
Pre-op pressors = 1	9/44 (20.5%)	
Pre-op pressors ⩾ 2	6/44 (13.6%)	
Red blood cell transfusion	11/44 (25.03%)	
Pre-op hemoglobin (g/dL)	11.7 ± 2.3	4.8-16.5
Pre-op mean arterial pressure (mmHg)	88.6 ± 17.8	57-121
Pre-op SpO_2 (%)	97.3 ± 5.4	65-100
Pre-op PaO_2 (torr)	181.9 ± 114.7	41-472
Pre-op arterial O_2 content (mL/100 mL)	16.0 ± 3.3	7.5-23.2
Donor hypoxia accrual time (min)	20.8 ± 5.5	9.0-33.0
Extubation-to-asystole time (min)	12.6 ± 5.2	4.0-24.0
Asystole-to-aortic clamp time (min)	8.2 ± 2.4	5.0-14.0
Donor ischemia time (min)	12.4 ± 6.1	2-25
Donor hypoxemia time (min)	14.2 ± 6.1	1-29
Donor hypoxia score	2.3 ± 1.1	0.4-4.8
Pre-donation length of stay (d)	3.8 ± 2.3	1-13
No arrest	24 (53.3%)	
Pre-donor duration of arrest (min)	31.5 ± 20.6	3-75

organization and/or by the abdominal transplant team at the University of Colorado Hospital. The OPO obtained consent for recovery and to administer 30000 units of intravenous heparin prior to extubation. Withdrawal of life support (*i.e.*, extubation and stoppage of vasopressor agents), institution of comfort measures, and declaration of death were in compliance with donor hospital policies (*i.e.*, either in the post-anesthesia care unit with rapid transport to the OR, or in the OR). Following declaration of death, a mandatory observation of 2-5 min was performed with reconfirmation of death, depending on the donor hospital policy.

Rapid retrieval was performed using aortic cannulation through an infrarenal approach, and portal cannulation through the inferior mesenteric vein, using University of Wisconsin solution or histidine-tryptophan-ketoglutarate cold solution. Once cold perfusion was initiated, the common bile duct was transected at the duodenum and the gallbladder was opened and flushed with saline, until the effluent from the transected duct was clear. Tissue plasminogen activator was flushed through the arterial system after the liver was excised, before packaging it in cold histidine-tryptophan-ketoglutarate. Because dosing and administration was attending-dependent, these were inconsistent.

Statistical analysis

Continuous variables are expressed as means ± standard deviations. Statistical relationships were performed using the following techniques: (1) *t*-test for comparison of interval continuous data between two groups; (2) Wilcoxon rank-sum test for comparison of ordinal-rank continuous data between two groups; (3) Pearson's correlation coefficient analysis to assess the relationship between two continuous variables; (4) Fisher's exact test to assess 2 × 2 contingency tables; and (5) logistic multivariate regression analysis to assess the impact of independent variables on binary response variables. SAS System for Windows, release 9.2 (SAS Institute Inc., Cary, NC, United States) was used to perform the statistical analysis. $P < 0.05$ represented statistical significance.

RESULTS

From February 2003 to September 2013, 45 consecutive patients underwent a DCD liver transplant. HC occurred in 50.0% (n = 22) of DCD liver recipients with 15.9% (n = 7) requiring re-transplantation. The 1, 3, and 5 year graft survival rates were 83%, 77%, and 60%, respectively. The 1, 3, and 5 year patient survival rates were 92%, 84%, and 72%, respectively.

Donor risk conditions for HC

One patient was excluded from the analysis secondary to an intraoperative death. Donor risk conditions are described in Table 1. The median age of DCD liver donors was 30 years old with a body mass index < 30 kg/m^2. Most donors did not receive RBC transfusion, were not on vasopressors, and did not suffer a pre-admission cardiac arrest.

Donor preoperative O_2 delivery and hc risk

Recipient HC univariate correlations with preoperative donor oxygen delivery are presented in Table 2. Patients not developing HC were younger, more frequently received preoperative multiple vasopressor administration and RBC transfusions, had higher preoperative hemoglobin and arterial O_2 content, and had lower preoperative MAP. Multivariate analysis showed that recipient HC was independently associated with increased MAP (P = 0.07), lower arterial O_2 content (P = 0.02), decreased multiple-pressor or RBC administration (P = 0.013), and older age (P = 0.11) (r^2 = 0.4427).

Eleven of 44 (25.0%) donors underwent preoperative RBC transfusion. The transfusion group had a lower initial pH (7.23), compared to the non-transfusion group (7.33; P = 0.03). The transfusion group had a normal preoperative pH (7.39), compared to their initial value (7.23; P = 0.001). The transfusion group had a lower initial SpO_2 (91.3%), compared to the non-transfusion group (97.3%; P = 0.007). The transfusion group had a similar preoperative hemoglobin (11.0 g/dL), when compared to the non-transfusion group (12.0 g/dL; P = 0.17).

Of the 44 donors, 6 (13.6%) received ⩾ 2 pressors during the preoperative period. Initially, the multi-pressor group was acidemic (pH 7.27 ± 0.18); yet, following the administration of multiple pressor agents the acidosis improved (pH 7.37 ± 0.09; P = 0.29).

Table 2 Hypoxic cholangiopathy correlations with preoperative donor oxygen delivery

	(-) Hypoxic cholangiopathy	(+) Hypoxic cholangiopathy	*P* value
n	22	22	
Age	25.6 ± 8.4	33.0 ± 10.6	0.020
Multiple pressor administration	27.3%	0.0%	0.009
RBC transfusion	36.4%	9.5%	0.040
RBC or multiple pressor administration	54.6%	9.5%	0.001
Hemoglobin	12.3 ± 2.1	10.7 ± 2.2	0.020
Arterial O_2 content (mL/100 mL)	16.8 ± 3.3	14.8 ± 2.8	0.049
Mean arterial pressure (mmHg)	83.8 ± 18.5	92.7 ± 16.2	0.100

RBC: Red blood cell.

Table 3 Comparison of patients with preoperative multiple pressors or red blood cell transfusion

	(-) Multiple-pressor/RBC	(+) Multiple-pressor/RBC	*P* value
n	29 (67.4%)	14 (32.6%)	
Hypoxic cholangiopathy	19 (65.5%)	2 (14.3%)	0.001
Initial pH	7.33 ± 0.14	7.25 ± 0.12	0.08
Pre-op pH	7.43 ± 0.06	7.39 ± 0.08	0.07
Initial PaO_2	156.4 ± 84.0	133.6 ± 117.6	0.48
Pre-op PaO_2	171.5 ± 106.1	191.2 ± 129.8	0.60
Initial SpO_2 (%)	97.5 ± 2.7	92.2 ± 9.9	0.012
Pre-op SpO_2 (%)	97.9 ± 2.0	95.9 ± 8.8	0.41
Initial P/F O_2	228.5 ± 116	191.4 ± 93	0.40
Pre-op P/F O_2	212.5 ± 101	243.8 ± 126	0.41
Initial PEEP (cmH_2O)	6.0 ± 2.7	5.6 ± 3.9	0.69
Pre-op PEEP (cmH_2O)	7.1 ± 4.6	7.0 ± 4.5	0.96
Pre-op hemoglobin (g/dL)	11.8 ± 1.9	11.8 ± 2.5	0.99
Arterial O_2 content (mL/100 mL)	16.2 ± 2.5	16.1 ± 4.0	0.93
Pre-op systolic pressure (mmHg)	133.6 ± 21.9	123.5 ± 26.8	0.19
Pre-op diastolic pressure (mmHg)	74.3 ± 15.7	64.3 ± 18.1	0.06
Pre-op mean pressure (mmHg)	92.1 ± 16.6	82.1 ± 19.2	0.08
Pre-op heart rate (bpm)	92.3 ± 20.2	96.9 ± 22.3	0.49

Complete data available for 43/45 (95.6%) patients. RBC: Red blood cell; PEEP: Positive end-expiratory pressure.

Initial SpO_2 was insignificantly higher in the non-multi-pressor group (96.6%), compared to the multi-pressor cohort (89.4%; P = 0.37), despite a mean PaO_2 of 120.4 ± 65.0 in the latter group. Following multi-pressor administration, the SpO_2 increased to 99.3% ± 0.8% (P = 0.24). The preoperative SpO_2 was higher in the multi-pressor group (99.3%), compared to the non-multi-pressor group (96.8%; P = 0.02). The preoperative P/F O_2 was higher in the multi-pressor group (305.3) compared to the non-multi-pressor group (210.8; P = 0.07); however, the PEEP levels were comparable (8.2 and 6.9 cmH_2O; P = 0.55). Multi-pressor use did not create preoperative hypertension (systolic BP 113.2 ± 22.1; diastolic BP 67.5 ± 16.3) or tachycardia (heart rate 105.0 ± 18.6).

A comparison of the preoperative RBC/multi-pressor group with the non-intervention group is presented in Table 3. The initial pH in the RBC/multi-pressor group was more acidemic, compared to the non-RBC/multi-pressor group. The RBC/multi-pressor group's preoperative pH was significantly higher, compared to their initial pH (P = 0.001). The RBC/multi-pressor group had a 51.3 torr increase in the preoperative PaO_2 relative to the initial PaO_2 (P = 0.22). The RBC/multi-pressor group's preoperative SpO_2 increased, compared to their initial value (P = 0.29). The RBC/multi-pressor group's preoperative P/F O_2 was insignificantly higher, compared to their initial P/F O_2 with an almost identical preoperative PEEP and preoperative hemoglobin, compared with the non-RBC/multi-pressor group. The non-RBC/multi-pressor group's preoperative P/F O_2 had a minimal decrease, compared to their initial P/F O_2. The increment from the initial P/F O_2 to the preoperative P/F O_2 in the two groups trended towards significance (P = 0.09).

Donor post-extubation hypoxia and HC risk

Recipient HC correlations with donor post-extubation hypoxia are presented in Table 4. Neither cold nor warm ischemia had a statistical association with HC. HC was not associated with the duration of donor hypoxia accrual, extubation-to-asystole, asystole-to-aortic clamping, donor ischemia, or donor hypoxemia times. HC was associated with donor preoperative hemoglobin and the donor hypoxia score. HC was associated with a donor hypoxia score > 2.0 (relative

Table 4 Hypoxic cholangiopathy correlations with donor post-extubation hypoxia

	(-) Hypoxic cholangiopathy	(+) Hypoxic cholangiopathy	*P* value
n	22	22	
Donor hypoxia accrual time (min)	20.3 ± 5.8	21.6 ± 5.2	0.470
Extubation-to-asystole time (min)	12.0 ± 5.1	13.4 ± 5.4	0.380
Asystole-to-aortic clamp time (min)	8.3 ± 2.6	8.1 ± 2.3	0.800
Donor ischemia time (min)	11.7 ± 7.4	13.5 ± 4.2	0.340
Donor hypoxemia time (min)	13.2 ± 6.5	15.5 ± 5.6	0.220
Preoperative hemoglobin (g/dL)	12.3 ± 2.1	10.7 ± 2.2	0.017
Donor hypoxia score	2.0 ± 1.2	2.7 ± 0.9	0.030
Donor hypoxia score > 2.0	25.0%	69.6%	0.006

Table 5 Recipient risk variables - *n* = 45 *n* (%)

	Result	Range
Hepatitis-C	13 (28.9)	
Ethanol	6 (13.3)	
Alpha-1 antitrypsin	9 (20.0)	
Hepatitis B	3 (6.7)	
Hepatocellular carcinoma	18 (40.0)	
⩾ 2 diagnoses	21 (46.7)	
MELD	28.7 ± 5.6	17-40
Duct to duct anastamosis	38 (84.4)	
Cold-ischemia time (min)	429.9 ± 127.3	60-660
Warm-ischemia time (min)	35.4 ± 13.6	16-76
Total-ischemia time (min)	465.6 ± 131.0	95-688

MELD: Model for end-stage liver disease.

Table 6 Era 1 and era 2 risk comparisons

	Era 1	Era 2	*P* value
DCD liver transplants	17	27	
Hypoxic cholangiopathy	29.4%	63.0%	0.030
Transplants per year	2.5	7.1	0.100
Hepatocellular carcinoma	23.5%	51.9%	0.060
Donor body mass index (kg/m^2)	24.1 ± 3.1	26.7 ± 4.3	0.030
Donor hypoxia accrual time (min)	17.3 ± 5.0	22.7 ± 4.8	0.001
Donor extubation-to-asystole time (min)	9.3 ± 4.5	14.4 ± 4.7	0.001
Donor aystole-to-crossclamp time (min)	8.1 ± 2.7	8.3 ± 2.3	0.779
Donor ischemia time (min)	9.7 ± 5.6	13.9 ± 5.9	0.030
Donor hypoxemia time (min)	11.1 ± 6.7	16.0 ± 5.1	0.013
Donor hypoxia score	1.6 ± 0.9	2.7 ± 1.1	0.003
Donor hypoxia score > 2.0	28.6%	73.1%	0.006
Recipient cold ischemia time (min)	381 ± 139	461 ± 111	0.040
Recipient warm ischemia time (min)	31 ± 10	39 ± 15	0.030
Recipient total ischemia time (min)	411.8 ± 135	499.4 ± 119	0.030

risk = 2.8). Multivariate analysis showed that the recipient HC was independently associated with increased donor age (P = 0.10), increased donor preoperative MAP (P = 0.06), decreased donor preoperative arterial O_2 content (P = 0.08), less donor preoperative RBC or multiple-pressor administration (P = 0.03), and a greater rate of donor hypoxia score > 2 (P = 0.06, r^2 = 0.6197).

Recipient risk conditions

Select recipient risk conditions are presented in Table 5. HC had no association with any of the conditions listed in the Table (P > 0.05).

Era 1 and era 2 donor preoperative O_2 delivery/post-extubation hypoxia and HC

Era 2 donors had a higher HC rate and more transplants per year, compared to era 1 (Table 6). A comparison of era 1 and era 2 showed that era 2 times were longer for donor hypoxia accrual, donor extubation-to-asystole, donor ischemia, donor hypoxemia, and recipient cold ischemia. Era 2 donors also had a higher donor hypoxia score and a higher rate for donor hypoxia scores > 2.0. The correlations for era 2 donors *vs* era 1 donors were greater for donor hypoxia score (r^2 = 0.2443) and extubation-to-asystole time (r^2 = 0.1839), when compared to donor cold ischemia time (r^2 = 0.1045). Multivariate analysis identified era 2 *vs* era 1 as independently associated with a greater donor hypoxia score > 2.0 rate (P = 0.04), a longer recipient cold ischemia time (P = 0.02), and longer extubation-to-asystole time (P = 0.07, r^2 = 0.3905).

Multivariate analysis showed that HC was independently associated with increasing age (P = 0.02), less preoperative RBC or multiple-pressor administration (P = 0.04), greater donor hypoxia score > 2.0 (P = 0.03), and era 2 (P = 0.06, r^2 = 0.6502). Cold ischemia times were the same for recipients not developing HC (432 m) and those acquiring HC (431 m, P = 1.0). Recipient warm ischemia times were also similar (33 m *vs* 39 m, P = 0.18).

DISCUSSION

Donor post-extubation hypoxia and recipient HC

We found, following withdrawal of life support, an association between recipient HC and lower donor hemoglobin and longer durations of donor diastolic BP < 60 mmHg (ischemic time) and donor SpO_2 < 80% (hypoxemic time) until aortic cold-perfusion and cross clamping. These findings are summarized by the significant association between recipient HC and the donor hypoxia score. The time until aortic cold-perfusion and cross clamping (donor hypoxia accrual time) following the withdrawal of life support was not associated with recipient HC. It is clear from the

data in our study that ischemic hypoxia or hypoxemic hypoxia did not occur for several minutes following life support withdrawal. That is, the average time from the withdrawal of life support until cross clamping exceeded the times for SpO_2 < 80% and diastolic BP < 60 mmHg.

The DCD liver transplant literature has historically and commonly referred to the donor hypoxia accrual time as the donor warm ischemic time (DWIT)[10]. Abt *et al*[11] have shown that this time period was not associated with graft survival in DCD liver transplantation. However, de Vera *et al*[12] has shown that DWIT > 20 min is associated with poor graft survival. More specifically, DeOliveira *et al*[7] demonstrated that DWIT does not correlate with biliary complications. Their group defined DWIT as the time from life support withdrawal until aortic cannulation, where the SpO_2 fell < 70% or systolic BP decreased < 50 mmHg. Their lack of correlation may be related to the failure to separately consider each as a hypoxic risk condition or that their criteria are too conservative. A meta-analysis by O'Neill *et al*[10] demonstrated that DWIT correlated with DCD HC; however, the definitions of DWIT in the published literature were variably defined. Taner *et al*[5] comprehensively examined DWIT and failed to show significant associations with overall biliary complications or intrahepatic bile duct strictures, despite using multiple criteria for critical hypotension and hypoxemia.

A review of the DCD liver transplant literature showed that interval definitions for DWIT have been variable and included the time from extubation to cold perfusion, cardiac arrest, or aortic cross-clamping, or was the time from arrest to hepatic perfusion[10]. We were unable to identify any study where the magnitude of ischemic and hypoxemic hypoxia were combined to assess correlation with adverse outcomes; relevant examples include the studies by Elaffandi *et al*[13], Skaro *et al*[14], and Ho *et al*[15]. Although a hemoglobin of > 10 mg/dL is recommended as a critical care donor management goal[16], we have not found literature that explored the potential effect of donor hemoglobin on DCD liver transplant outcomes.

Relevant to our study observations are multiple etiologic factors for hepatic hypoxia, including ischemia, arterial hypoxemia, and severe anemia[17-19]. Two publications emphasize that decreased hepatic blood flow is not the sole mechanism of hypoxic liver injury, and therefore hypoxic hepatitis or hypoxic liver injury is more appropriate terminology[19,20]. These literature findings support study observations that the ischemic, hypoxemic, and anemic elements of the donor hypoxia score are clinically reasonable.

Also relevant to the study finding that the donor hypoxia score correlated with HC is the recognized physiologic concept of systemic oxygen delivery, with constitutive elements of ischemia, hypoxemia, and anemia. Although the investigation by Kostopanagiotou *et al*[21] emphasized the importance of oxygen delivery during orthotopic liver transplantation, the concepts are applicable to the issue of donor hypoxia. Systemic tissue oxygen delivery depends on an adequate cardiac output and arterial oxygen content, where the latter is affected by SaO_2 and hemoglobin. Of importance, MAP is directly related to cardiac output and systemic vascular resistance[22,23]. Thus, critical decreases in cardiac output or BP (ischemic hypoxia), SaO_2 (hypoxemic hypoxia), or hemoglobin (anemic hypoxia) cause cellular hypoxia and lactic acidosis[24-26].

Based on the aforementioned line of reasoning and our study findings, we suggest the historic term DWIT is ambiguous relative to time intervals, and does not fully encompass the three physiologic elements that can interactively cause cellular hypoxia. Since elements of hypoxia other than ischemia are present, the historic use of DWIT is not an adequately descriptive term. Because there is no donor cold ischemic or hypoxic period, it is unnecessary to include the word warm in the definitive terms. We propose that the historic DWIT be changed to donor hypoxia accrual time, which is the time from the withdrawal of life support until aortic cold-perfusion and cross clamping. We recommend that donor ischemia time represent the number of minutes from the onset of diastolic BP < 60 mmHg, following life support withdrawal, until aortic cold-perfusion and cross clamping. Finally, we suggest donor hypoxemia time be used to signify the number of minutes elapsing from the onset of SpO_2 < 80%, following life support withdrawal, until aortic cold-perfusion and cross clamping. The study findings indicate that the donor hypoxia score, an interactive variable that includes donor ischemia time, donor hypoxemia time, and preoperative hemoglobin, can be used to assess the DCD post-transplantation risk for recipient HC.

Donor preoperative O_2 delivery and recipient HC

Donor characteristics of younger age, higher preoperative hemoglobin, greater preoperative arterial O_2 content, lower preoperative MAP, and greater preoperative RBC/multi-pressor use were associated with decreased recipient HC. We reason that donor age was a significant finding because older patients have increased celiac axis[27] and thoracic and abdominal aortic atherosclerotic occlusive disease[28,29] and reduced cardiac output[30,31] that can affect hepatobiliary perfusion. Thus, it seems feasible that donors with a lower age and higher hemoglobin would have better preoperative hepatobiliary oxygen delivery that potentially reduces the risk for HC. Of relevance, donor ejection fraction of > 50% is a critical care donor management goal[32], that has been shown to be associated with an increase in successful organ transplantation[16]. Multiple investigators have shown that lower donor age has been associated with a reduction in DCD liver transplantation overall biliary complications[12], non-anastomotic biliary stricture[33], graft failure[2],

and HC[10,34]. This explains why pre-transplantation hemoglobin > 10 g/dL is recommended as a critical care donor management goal[16]. Our study showed that a preoperative donor hemoglobin > 12.0 gm/dL correlated with less HC.

The current investigation showed that the pre-operative RBC/multi-pressor group had a reduction in HC. The RBC group was initially more acidemic and had a lower SpO_2 compared to the non-RBC group. Following RBC transfusion, the preoperative pH improved into a normal range. The preoperative RBC group hemoglobin was comparable to those without transfusion, this suggesting that RBC transfusion was not excessive or inadequate. Of relevance, Pape *et al*[35] indicate that the decision to administer a blood transfusion should be based on clinical judgment relative to the individual's risk/benefit ratio associated with transfusion and anemia.

The donor multi-pressor group in the current study initially was severely acidemic and had a mean SpO_2 < 90%, despite a hyperoxemic PaO_2, findings suggesting the presence of shock[36] and hypotension[37]. Following the administration of multiple vasopressors, the preoperative pH and SpO_2 increased to normal ranges. Interestingly, the preoperative SpO_2 was higher in the multi-pressor group, compared to the non-multi-pressor group. It is further noteworthy that the preoperative P/F O_2 was higher in the multi-pressor group, compared to the non-multi-pressor group, despite comparable PEEP levels. Further, the multi-pressor group at the time of donor procurement did not have hypertension or tachycardia, suggesting that clinically-targeted vasopressor titration had been used.

It is important to note that a MAP of 60-100 mmHg has been established as a critical care donor management goal for successful organ transplantation[16,32]. The administration of vasopressors in organ transplant donors is controversial and Critical Care Donor Management Goal recommendations imply that the number of pressors should be limited to only one and that low-doses should be used[16,32]. However, these recommendations have been primarily based on an experience with brain-dead donors. One experience indicates that the vasopressor agent frequency is lower among DCD donors (9.4%) compared to brain-dead donors (74.7%; $P = 0.001$)[14]. Another investigation of 110 DCD donors showed that the number of vasopressors was not associated with graft survival[11]. A study by Feng *et al*[38] did not demonstrate a negative impact of donor hypotension or use of vasopressors on hepatic graft failure, by either univariate or multivariate analyses. In fact, in a review publication on DCD, Morrissey states "vasopressor use has improved outcomes that now approximate DBD liver transplantation"[39].

Relevant to a discussion regarding the use of vasopressors, it should be noted that hemodynamic instability and hypotension occur in 21%-82% of critically ill patients in an ICU[3,40,41] and the need for vasopressors has ranged from 24%-45%[3,40]. It is also germane that approximately 50% of hypotensive ICU patients will not respond to fluid administration; thus, it is imperative to determine which hypotensive patients will be responsive to fluid infusion[42,43]. Apropos, critically ill patients have hemodynamic instability typically based on one of three pathogenic mechanisms: cardiogenic (impaired contractility or altered heart rate), hypovolemic (intravascular volume deficiency), or distributive (vasogenic decrease in peripheral arterial tone)[43-45]. Appropriate patient assessment for these three states is critical in that appropriate intervention is predicated on the pathophysiology of the hemodynamic instability: fluids for hypovolemic, inotropes and echocardiography for cardiogenic, and vasopressors for distributive-vasogenic shock[42,45]. Multiple reliable devices can assist the intensivist in determining the presence of hypovolemic, cardiogenic, or distributive-vasogenic hemodynamic instability[42,46]. When hemodynamic instability fails to improve with volume-loading, inotropic-administration, or vasopressor-support, adrenal insufficiency and hypothyroidism of critical illness should be seriously considered[47].

Although the use of vasopressors is controversial for the management of hemodynamic instability, liver transplant patients commonly need inotropes and vasopressors during surgery[8,48], which reduce blood loss and lactic acidosis[8] and lessen need for tracheal re-intubation in the postoperative period[49]. An appropriate vasopressor MAP target of 60-65 mmHg has been suggested, without any clinical value for higher levels[22,44].

A couple of observations regarding arterial oxygenation are noteworthy relative to the RBC/multi-pressor group. First, the group had a clinically substantial increase in the preoperative PaO_2, relative to the initial value. Second, the group initially had a SpO_2 in the low-90s range which increased to the mid-90s following RBC transfusion or the administration of multiple pressors. Third, the P/F O_2 preoperative increment relative to the initial value in the RBC/multi-pressor group was substantially greater, compared to the non-treatment group. These findings indicate that improvements in arterial oxygenation, and thus potentially greater hepatobiliary tissue oxygen delivery, were better realized in the RBC/multi-pressor group. This potentially helps to account for the reduction in HC rates observed with these interventions.

The current study observations do not necessarily imply that donor candidates for DCD liver transplantation should carte blanche receive routine RBC transfusion or multiple vasopressors. The study findings do imply that it is reasonable in potential donor candidates with acidemia and anemia or vasogenic hemodynamic instability to provide RBC transfusion or administer vasopressors, respectively. The findings also indicate

that patients with positive physiologic responses to the interventions should be considered as acceptable DCD liver transplant donors. One can only speculate as to the reason patients receiving RBC transfusion or multiple pressors had a reduced rate of HC. It seems likely to be related, in part, to the selection of patients who are stabilized, based on objective physiologic and metabolic evidence. It also seems plausible that an astute intensivist may not only positively impact a circulatory deficiency, but also provide comprehensive care that maximally stabilizes other physiologic and metabolic systems. It is plausible that multiple pressors or RBC transfusion, in select donor patients, enhance systemic oxygen delivery and likely pre-procurement hepatobiliary oxygenation. The validity of these speculations is based on their linkage with a decreased rate of recipient HC.

Multivariate analysis showed that recipient HC was independently associated with a lower donor preoperative arterial O_2 content, older donor age, increased donor preoperative MAP and infrequent use of donor multiple pressors or RBC transfusions. The lower arterial oxygen content indicates that the interaction of hemoglobin, SaO_2, and PaO_2 likely mitigated systemic, and presumably hepatobiliary, oxygen delivery. As stated previously, it is likely that an older donor age could potentially decrease hepatobiliary blood flow due to a lower cardiac output or greater atherosclerotic occlusive disease. Although patients without HC had a lower donor preoperative MAP, compared to those developing HC, the average value remained in the normal range. Although precise, optimal MAP targets are uncertain, a MAP target recommendation for septic shock is 65 mmHg[50]. The current study's findings demonstrated an increased donor preoperative MAP in those developing recipient HC, suggesting that a higher MAP of 90 mmHg may be an undesirable target for young critically ill patients. It is plausible that an increased MAP in recipient HC patients emanates from higher preoperative peripheral arterial resistance and a reduction in cardiac output, thus impeding systemic, tissue oxygen delivery.

Era 1 and era 2 donor preoperative O_2 delivery/post-extubation hypoxia and HC

The transplants per year in era 2 represent a nearly 3-fold increase, compared to era 1. Our more liberal selection criteria was manifest by longer donor extubation-to-asystole, donor ischemia, and donor hypoxemia times and a higher donor hypoxia score and an increased donor hypoxia score > 2.0 rate in era 2. Although the recipient cold ischemia time in era 2 was increased compared to era 1, HC did not correlate with the recipient cold ischemia time. Further, the recipient cold ischemia time in era 2 is comparable to those reported by other United States liver transplantation centers[2]. The independent association of era 2 with HC, after controlling for donor age, multi-pressors/RBC transfusion status, and donor hypoxia score, suggests that donor selection criteria influence the subsequent development of recipient HC.

A direct relationship was observed with longer recipient warm ischemic times in era 2, compared to era 1, however this did not correlate with recipient HC. Although not statistically significant, more recipients in era 2 were transplanted for hepatocellular carcinoma, and whether the longer warm ischemic times are related to the quality of the recipient's hepatic artery is unknown. However, we do believe it is important to re-perfuse the hepatic veins and the portal vein prior to starting the arterial anastomosis to decrease further hypoxic injury to the biliary system, as confirmed by Farid *et al*[51]. Furthermore, moving forward ("Era 3"), our donor selection is comparable to era 1 with the use of tissue plasminogen activator (TPA) through the hepatic artery upon reperfusion, as recently demonstrated by Seal *et al*[52].

Limitations

Several methodological limitations need consideration. Although this is a retrospective study, this is an analysis of consecutive DCD liver transplants performed by identifying risk factors for the development of hypoxic cholangiopathy and we consider the UNOS DonorNet, DCD OR flow sheet, and University of Colorado's transplant database to be reliable. However, data accuracy and quality from a retrospective, database source are recognized to be lower, when compared to a prospective, dedicated database. Another limitation is the lack of consistency among the definition of donor warm ischemic time; however, we believe that this is a misnomer and should be called donor hypoxia accrual time. Also, we did not evaluate cross clamp time to liver in ice time. However, our aystole-to-cross clamp times were similar between era 1 and era 2, and we believe that explantation of the donor liver would yield similar results. Despite our limitations, to our knowledge, this is the only study to evaluate and define donor ischemia and hypoxemia time, preoperative donor hemoglobin, donor preoperative arterial O_2 content, and donor RBC transfusion requirements along with vasopressor administration so stringently.

In conclusions, HC continues to be a major morbidity of DCD liver transplantation. Our study indicated that HC was greater with an increased donor age, less donor preoperative multiple vasopressors or RBC transfusion, lower donor pre-operative hemoglobin, lower donor preoperative arterial oxygen content, and increased MAP. Higher donor pre-operative hemoglobin of 12 gm/dL is recommended prior to extubation. However, we do not recommend using vasopressors when not clinically indicated. Donor hypoxia score [a measurement of (donor ischemia time + donor hypoxemia time) ÷ donor pre-operative hemoglobin] provides an objective measure of DCD post-liver

transplantation risk for the development of recipient HC. The study also suggests that donor selection criteria have an impact on the proclivity for acquiring recipient HC.

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COMMENTS

Background

Orthotopic liver transplantation remains the gold standard for patients with end stage liver disease. The critical shortage of brain-dead organ donors has increased the utilization of donation after circulatory death (DCD) liver grafts. Many studies have compared donation after brain death to DCD liver transplants and have noted either inferior or comparable graft survival and biliary complications in the DCD group. Brain-dead donors, unlike DCD donors, do not experience an agonal phase where hepatobiliary hypoxia accrues. Taner *et al* stated that events during DCD procurement, such as variations in hemodynamics, a mandatory wait period, or time from incision to cross clamp, all included in the donor warm ischemic time, may impact the outcome of DCD liver transplants. The relative contribution of these factors on donor graft and recipient outcome is unknown.

Innovations and breakthroughs

The primary purpose of this study was to assess the effect of DCD donor risk conditions (age, hemodynamics prior to and after extubation, the use of vasopressors or red blood cell transfusions, preoperative hemoglobin, and pre-operative oxygen delivery) on development of hypoxic cholangiopathy (HC). The secondary aim was to evaluate the different eras of donors to see if these factors were predictive of recipient HC.

Applications

The present research indicates that cholangiopathy is linked to the magnitude of hypoxemic, ischemic, and anemic hypoxia transpiring after life support withdrawal and can be represented by a donor hypoxia score. The authors recommend that the historically utilized nomenclature of ischemic cholangiopathy be replaced using a more physiologic-based and expansive term, hypoxic cholangiopathy. Easily measured donor indices, including a hypoxia score, provide an objective measure of DCD liver transplantation risk for recipient HC. Donor selection criteria influence HC rates.

Peer-review

The authors face with the serious complication of hypoxic colangiopathy after liver transplantation using donors after circulatory death. In particular they analyze the different factors responsible for HC. Even if retrospective the study is well conducted with an excellent statistical analysis. In addition the study is well written, updated and give the reader useful clinical informations.

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