Liver Transplant From Controlled Cardiac Death Donors Using Normothermic Regional Perfusion: Comparison With Liver Transplants From Brain Dead Donors

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ABSTRACT

Background. Liver transplantation from donors after either controlled or uncontrolled cardiac death (DCD) is associated with considerable rates of primary nonfunction (PNF) and ischemic cholangiopathy (IC). Normothermic regional perfusion (NRP) could significantly reduce such rates.

Methods. Retrospective study to analyze short-term (mortality, PNF, vascular complications) and long-term (IC, survival) complications in 11 liver transplants from controlled DCDs using NRP with extracorporeal membrane oxygenation (ECMO) (group 1). They were compared with 51 patients transplanted with grafts from donors after brain death (DBD) (group 2). Mean recipient age, sex, and Model for End-stage Liver Disease (MELD) score were not significantly different.

Results. In group 1, mean functional warm ischemia time was 15.8 (range, 7–40) minutes and 94.1 (range, 20–150) minutes on NRP. The ischemic damage was minimal, as shown by the slight alanine aminotransferase (ALT) and aspartate aminotransferase (AST) rises in the donor serum after 1 hour on NRP and similar rises 24 hours after transplantation in both groups. No patient had IC or acute renal failure. No significant difference was found between the groups for vascular or biliary complications. One group 1 patient had PNF (9.1%), resulting in death. Overall retransplantation and in-hospital death rates were 8.1% and 4.8%, respectively, with no significant difference between groups. Estimated mean survival was 24.6 (95% confidence interval [CI], 20.2–29.1) months in group 1 and 32.3 (95% CI, 30.4–34.2) months in group 2 (not a statistically significant difference).

Conclusion. In our experience, liver transplants from controlled DCDs using NRP with ECMO is associated with a low risk of PNF and IC, with short- and long-term results comparable to those in DBD transplants.

THE GROWING need for organ transplantation, including liver, together with the shortage of cadaveric donors, has led to the search for new sources of organs. One of these is donation after cardiac death (DCD), either uncontrolled (Maastricht II) or controlled (Maastricht III) [1].

In the case of liver transplants, however, warm and cold ischemia times—usually longer with the resultant tissue hypoxia—make some postoperative complications more probable, such as ischemic cholangiopathy (IC) or graft primary nonfunction (PNF) [2,3]. When compared with liver transplants from donors after brain death (DBDs), significantly more IC, PNF, and retransplantations occurred in DCD patients [4].

IC is due to the special sensitivity of the biliary tree to hypoxia, with frequencies ranging from 3% [2] to 16% [3].

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0041-1345/18
https://doi.org/10.1016/j.transproceed.2018.04.067

Table 1A. Donor and Matched Recipient Features

Group/Patient	Donor Sex	Donor Age (Years)	Donor BMI	Cause of Death	Recipient Sex	Recipient Age (Years)	Recipient BMI	MELD	Indication
1/1	M	51	28.2	Lung fibrosis	F	28	22.2	24	Autoimmune cirrhosis
1/2	M	65	28.3	Complicated lung transplantation	F	58	31.2	6	CHV+HCC
1/3	F	61	24	Stroke	M	53	26	14	Alcohol
1/4	M	58	27.2	Complicated lung transplantation	M	62	28.73	9	Alcohol
1/5	F	54	24.1	Stroke and myocardial infarction	F	36	22.2	6	Sclerosing cholangitis
1/6	F	58	24	Stroke	M	64	28.1	31	Alcohol+hemochromatosis
1/7	F	65	24.2	Stroke	M	68	25.5	13	Alcohol+HCC
1/8	M	36	24.1	Stroke	F	60	24.2	20	Alcohol+HCC
1/9	F	51	22.5	Anoxic encephalopathy	M	62	25.3	16	Alcohol
1/10	M	36	27.5	Brain trauma	F	62	27	6	Alcohol+HCC
1/11	M	14	20.8	Stroke	F	55	26	17	Alcohol
2/1	F	76	22.1	Stroke	M	54	26.8	10	CHV+HCC
2/2	M	77	23	Stroke	M	42	22.9	2	Caroli disease
2/3	F	14	23	Brain trauma	F	14	17.5	29	Acute failure unknown origin
2/4	M	63	27	Brain trauma	M	38	19.3	16	Autoimmune cirrhosis
2/5	F	84	27	Stroke	M	53	34.5	19	Alcohol
2/6	M	48	24.6	Anoxic encephalopathy	M	48	31.2	22	CHV+alcohol
2/7	F	78	37.1	Stroke	M	60	31.4	14	Alcohol
2/8	F	77	24.8	Stroke	M	58	16.7	15	Hemochromatosis
2/9	M	23	25.5	Anoxic encephalopathy	M	65	27.8	21	Alcohol
2/10	F	30	18.5	Hypoglycemia	M	58	23.5	20	CHV+HCC
2/11	M	64	27.2	Stroke	M	58	21.9	22	Alcohol
2/12	M	67	27.1	Stroke	M	61	24.2	13	Posttransplant cirrhosis
2/13	M	53	25.5	Stroke	F	49	22.9	12	CHV+alcohol
2/14	F	82	29	Stroke	M	63	22.6	10	Alcohol
2/15	M	67	24.8	Stroke	M	46	27.4	23	Alcohol
2/16	F	56	25.6	Stroke	M	65	29.7	19	Alcohol
2/17	F	76	22.7	Stroke	M	63	26	9	Alcohol+HCC
2/18	F	71	25.4	Stroke	M	64	22	7	CHV+HCC
2/19	F	81	29.1	Stroke	M	63	33.8	9	Alcohol+HCC
2/20	F	77	23.9	Stroke	M	63	22.9	11	Posttransplant biliary tract necrosis
2/21	M	79	25.4	Stroke	M	51	28.4	6	CHV+HCC
2/22	F	65	30.9	Stroke	M	60	23.9	6	CHV+HCC
2/23	F	71	25.4	Stroke	M	57	20	10	CHV+HCC
2/24	F	64	29.1	Stroke	M	52	22.6	15	Posttransplant biliary tract necrosis
2/25	F	59	29.8	Stroke	M	61	26.7	14	Alcohol
2/26	F	75	24.2	Stroke	M	63	21.5	8	CHV+HCC
2/27	M	48	24.3	Brain trauma	F	55	37.8	19	Primary biliary cirrhosis
2/28	F	85	25.1	Stroke	M	66	24.3	9	Alcohol+HCC
2/29	F	75	30.8	Stroke	M	56	26.4	8	Alcohol
2/30	F	84	24.2	Stroke	M	62	26.4	20	CHV+HCC
2/31	M	67	24.2	Stroke	F	33	25.7	14	Autoinmune cirrhosis
2/32	M	81	25	Stroke	M	63	20.3	10	Alcohol
2/33	M	67	24.1	Stroke	M	50	27.2	9	Neuroendocrine metastases
2/34	F	59	29	Stroke	M	62	29.7	23	HCC
2/35	M	45	25.1	Stroke	M	45	29	8	Sclerosing cholangitis
2/36	M	67	24	Brain trauma	M	67	23.9	14	Alcohol
2/37	F	70	29.8	Stroke	M	65	34.9	9	Alcohol+HCC
2/38	M	64	24	Stroke	M	67	32.9	7	HCC
2/39	F	58	23.1	Stroke	M	47	20.2	12	Sclerosing cholangitis
2/40	F	67	23.2	Stroke	F	60	21.9	14	Alcohol
2/41	M	79	27	Stroke	F	55	25.3	24	Alcohol
2/42	M	68	26	Stroke	M	61	24.2	11	CHV+HCC

Table 1A. (continued)

Group/Patient	Donor Sex	Donor Age (Years)	Donor BMI	Cause of Death	Recipient Sex	Recipient Age (Years)	Recipient BMI	MELD	Indication
2/43	M	58	26.5	Stroke	M	48	36.1	13	CHV+HCC
2/44	M	79	27.5	Stroke	M	44	22.6	21	BVH+DVH
2/45	F	52	26.7	Stroke	F	60	27.9	15	CHV
2/46	M	70	30.2	Stroke	M	63	34.3	9	Alcohol+HCC
2/47	F	53	20.8	Stroke	M	66	24.1	24	Alcohol
2/48	M	22	25.8	Brain trauma	M	58	21	12	BVH+HCC
2/49	M	77	24.5	Brain trauma	M	56	28.4	17	Alcohol
2/50	M	81	31	Stroke	M	48	28	13	HCC
2/51	M	30	20.4	Brain trauma	F	54	27.1	18	Alcohol

Abbreviations: BMI, body mass index; BVH, B virus hepatitis; CHV, C virus hepatitis; HCC, hepatocellular carcinoma; MELD, Modified End-stage Liver Disease (score).

To diminish the hypoxia, normothermic regional perfusion (NRP) using extracorporeal membrane oxygenation (ECMO), between the cardiac arrest and the beginning of organ procurement, has been proposed. Clinical and experimental data support its use in uncontrolled donors to better maintain liver function, showing additional benefits over traditional cold storage [5]. Results in controlled donors have also been promising, with low rates of both IC and PNF [6]. In Spain, the first liver transplant using NRP in a controlled DCD was reported in 2014 [7].

The aim of this work was to report our initial experience with liver transplants with controlled DCD using NRP with ECMO in a comparison with outcomes for DBD, performed in the same period.

MATERIALS AND METHODS

From September 2014 to March 2017 liver transplantation was performed with DCD in 11 patients (group 1) and 51 with DBD (group 2) at the University Hospital "Marqués de Valdecilla" (Santander, Spain). Seven patients were included in a previous general overview of DCD at the same center [8]. Our inclusion criteria for liver transplantation in the case of DCD are the same as those of DBD and, in addition, they had to fulfill the following conditions: donor age <70 years; functional warm ischemia <30 minutes; warm ischemia <90 minutes; donor aspartate aminotransferase/alanine aminotransferase (AST/ALT) serum levels <3 times the normal values; and absence of liver disease based on a normal ultrasound and AST/ALT serum levels.

Warm ischemia was defined as the time between life support withdrawal, including extubation, and the beginning of the preservation procedure (start of NRP). Functional warm ischemia, or agonal time, was defined as the time from the systolic pressure drop <60 mm Hg and the beginning of the preservation procedure, 5 minutes after cardiac arrest. Cold ischemia was defined as the time between the start of cold infusion of the graft to the clamping relief of the recipient portal vein.

The protocol was as follows: upon family information and acceptance of the life support limitation, informed consent for donation and premortem cannulation and heparin administration was obtained. The procedure is performed in the intensive care unit, in the presence of relatives if so desired. In addition to cannulation through the femoral artery, a deflated aortic balloon is inserted to isolate the abdominal and thoracic circulation. After cardiac arrest, there is a waiting time of 5 minutes to avoid autoresuscitation, in accordance with to the Spanish law. Then, the aortic balloon is inflated and NRP starts at 37°C, with a flow of 2.2–2.4 L/min. The donor is taken to the operating room for the procurement procedure, which is performed using a standard technique [9]. University of Wisconsin solution is used. The graft is also implanted with a standard technique of caval preservation [10]. Biliary anastomosis is done between the donor hepatic duct and the recipient choledochus. In 1 patient with sclerosing cholangitis, a Roux-en-Y hepaticojejunostomy was done for biliary reconstruction.

DCDs included 5 women and 6 men, with an average age of 49.9 (range, 14–65) years. Mean body mass index (BMI) was 24.9 (SD, 2.5). The cause of death and other clinical data are shown in Table 1A and 1B. All procurement procedures were local, except in 1 instance.

DBDs included 26 women and 25 men with an average age of 64.4 (range, 14–85) years. Donor age was significantly lower in group 1 than in group 2 ($P = .01$). Mean BMI was 25.9, not significantly different from group 1 ($P = .4$). Thirty-three procurement procedures were local and 18 were from other regional centers. The cause of death was a stroke in 42 (82.4%), head trauma in 6 (11.8%), anoxia after cardiac arrest in 2 (3.9%), and hypoglycemic coma in 1 (2%).

DCD recipients (group 1) included 5 men and 6 women, with a mean age of 55.3 (SD, 12.3; range, 28–68 years), with a mean BMI of 26 (SD, 2.8) and a mean Model for End-stage Liver Disease (MELD) score of 14.7 (SD, 8). DBD recipients included 43 men and 8 women, with a mean age of 55.6 (SD, 10.1; range, 14–69) years, a mean BMI of 26 (SD, 4.8), and a mean MELD score of 14 (SD, 5.8). No significant difference was found in BMI, MELD score, or recipient age between the 2 groups, although the proportion of men in group 2 was significantly higher. Recipient mean MELD score was not significantly different: 14.7 (range, 6–31) in group 1 and 14 (range, 2–29) in group 2.

The outcome measures were postoperative complications including: 1. vascular complications, specifically arterial or venous thrombosis found on postoperative ultrasound, and arterial disruption or pseudoaneurysms; 2. PNF, when, consistent with the Olthoff criteria [11], 1 or more of the following variables were present—a. bilirubin >10 mg/dL on postoperative day 7, b. international normalized ratio (INR) >1.6 on postoperative day 7, or c. aminotransferase levels (ALT or AST) >2000 IU/mL within the first 7 postoperative days; (iii) IC, defined as a diffuse stenosis of the intrahepatic biliary tree, as suspected by jaundice, cholangitis, abnormal biochemical liver test, or abnormal findings on ultrasound

Table 1B. Posttransplant Outcomes

Group/Patient	Primary Failure	Artery Thrombosis	Ischemic Cholangiopathy	Acute Renal Failure	Postoperative Death	Retransplant
1.1	N	N	N	N	N	N
1.2	N	N	N	N	N	N
1.3	N	N	N	N	N	N
1.4	N	N	N	N	N	N
1.5	N	N	N	N	N	N
1.6	N	N	N	N	N	N
1.7	N	Y	N	N	N	N
1.8	Y	–	–	–	Y	–
1.9	N	N	N	N	N	N
1.10	N	N	N	N	N	N
1.11	N	N	N	N	N	N
2.1	N	N	N	Y	N	N
2.2	N	N	N	N	N	N
2.3	Y	N	N	N	N	N
2.4	N	N	N	N	N	N
2.5	N	N	N	N	N	N
2.6	N	N	N	Simultaneous LKTx	N	N
2.7	N	Y	N	Y	N	N
2.8	N	N	N	N	N	N
2.9	N	N	N	N	N	N
2.10	N	N	N	Y	N	N
2.11	N	N	N	N	N	N
2.12	N	N	–	Y (septic shock)	Y	–
2.13	N	N	N	N	N	N
2.14	N	Y	N	N	N	N
2.15	N	N	N	N	N	N
2.16	N	N	N	Y	N	N
2.17	N	N	N	Y	N	N
2.18	N	N	N	N	N	N
2.19	N	N	N	Y	N	N
2.20	N	Y	N	N	N	N
2.21	N	N	N	N	N	N
2.22	N	Y	N	N	N	N
2.23	N	N	N	N	N	N
2.24	N	N	N	Y	N	N
2.25	N	Y	N	Y	N	N
2.26	N	N	N	N	N	N
2.27	N	N	N	N	N	N
2.28	N	N	N	Y	N	N
2.29	N	N	N	N	N	N
2.30	N	N	N	Y	N	N
2.31	N	N	N	N	N	N
2.32	N	N	N	Y	N	N
2.33	N	N	N	Y	N	N
2.34	N	N	N	Y	N	N
2.35	N	Y	–	Y	Y	–
2.36	N	N	N	Y	N	N
2.37	N	N	N	Y	N	N
2.38	N	N	N	N	N	N
2.39	N	N	N	N	N	N
2.40	N	N	N	Y	N	N
2.41	N	N	N	Y	N	N
2.42	N	N	N	N	N	N
2.43	N	Y	N	N	N	Y
2.44	N	N	N	Y	N	N
2.45	N	N	N	Y	N	N
2.46	N	N	N	N	N	N

Table 1B. (continued)

Group/Patient	Primary Failure	Artery Thrombosis	Ischemic Cholangiopathy	Acute Renal Failure	Postoperative Death	Retransplant
2.47	N	N	N	N	N	N
2.48	N	Y	N	Y	N	N
2.49	N	N	N	N	N	N
2.50	N	N	N	N	N	N
2.51	N	N	N	N	N	N

Abbreviations: F, female; LKTx, liver-kidney transplant; M, male; N, no; Y, yes.

or T-tube cholangiography—provided there is no hepatic artery thrombosis [2]; and (iv) acute renal failure, defined as peak serum creatinine ≥2 times the baseline level.

For statistical analysis, the chi-square test was used for comparison of discrete variables, means and analysis of variance for continuous variables, and Kaplan-Meier and log-rank tests for survival.

RESULTS

In group 1, the mean time of warm ischemia was 31.4 (range, 16–78) minutes and time of functional warm ischemia was 15.8 (range, 7–40) minutes (Table 2). The mean time on NRP was 94.1 (range, 20–150) minutes. One of the cases was only 20 minutes on NRP in the setting of combined procurement of liver and lungs, with a dramatic drop in the ECMO flow after vena cava clamping with the resulting need for shortening the procedure. Because liver perfusion had been satisfactory, the graft was considered suitable for transplantation. The mean time on NRP, excluding this case, was 101.5 (range, 47–150) minutes. The ischemic damage of the liver was minimal, according to the slight increase in mean ALT and AST values in the donor blood after 1 hour or NRP 54 (range, 13–115) U/L and 53 (range, 21–115) U/L, respectively.

The mean value of cold ischemia time in group 1 was 243.6 (range, 147–375) minutes, and 334.3 (range, 145–665) minutes in group 2 ($P = .009$).

Recipient serum ALT and AST values exhibited an initial increase, and then gradually decreased. Twenty-four hours after transplantation, the AST and ALT peaks were 520 U/L and 339 U/L in group 1 and 717 U/L and 653 U/L in group 2, respectively (NS), indicating similar ischemia/reperfusion damage.

The overall retransplantation rate was 8.1%, none in group 1 and 9.8% in group 2 (NS). The overall in-hospital death rate was 4.8%: 9.1% in group 1 and 3.9% in group 2 (NS).

Short-term Morbidity

In group 1, the serum bilirubin values were <10 mg/dL and international normalized ratio (INR) was <1.6 in all cases except 1; thus, according to the Olthoff criteria [11], only 1 case developed PNF (Table 3). This case rapidly evolved into universal bleeding that resulted in death. Among the survivors, 1 case of early hepatic artery thrombosis and no case of portal vein thrombosis was observed, as shown by the ultrasound routinely performed in the postoperative period. There were 3 cases of abdominal hemorrhage leading to reoperation: 1 in a branch of the common hepatic artery of the graft, 1 at the anastomosis cava-cava; and 1 at the Roux-en-Y jejuno-jejunostomy suture line. There were no cases of renal failure. There were 3 biliary leaks (27.3%). The minimum follow-up was 3 months in every case.

When compared with group 2, no significant difference was found for early hepatic artery thrombosis, portal thrombosis, pseudoaneurysm or disruption of the hepatic artery, or biliary leak. However, significantly more patients had acute renal failure in group 2 (42.9%) than in group 1 (none), even after excluding 1 patient with a double liver-kidney transplant and another with acute renal failure clearly related to septic shock.

Table 2. Clinical Data for Group 1 Recipients

Case	Functional Warm Ischemia (min)	Time on ECMO (min)	Cold Ischemia (min)	AST/ALT 24 Hours (U/L)	AST/ALT Day 5 (U/L)	Follow-up
1	12	129	240	137/160	61/133	27 months; alive; functioning graft
2	22	125	275	1763/731	217/886	26 months; alive; functioning graft
3	10	140	260	579/642	24/14	18 months; alive; functioning graft
4	12	102	235	163/120	86/242	26 months; alive; functioning graft
5	17	20	217	649/399	44/172	30 months; alive; functioning graft
6	10	47	375	472/274	32/78	18 months; alive; functioning graft
7	40	97	225	54/38	76/222	19 months; alive; functioning liver and kidney grafts
8	12	40	285	–	–	Primary failure; dead; postoperative day 1
9	17	150	147	168/128	98/177	11 months; alive; functioning graft
10	9	128	270	806/529	17/109	7 months; alive; functioning graft
11	7	57	150	156/185	103/376	7 months; alive; functioning graft

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ECMO, extracorporeal membrane oxygenation.

Table 3. Comparison of Surgical Outcomes Between Groups 1 and 2

	Group 1	Group 2	*P* Value
Primary liver failure	1 (9.1%)	1 (2%)	.3
Early arterial thrombosis	1 (9.1%)	8 (15.7%)	.5
Delayed arterial thrombosis*	1 (10%)	3 (6.1%)	.5
Anastomotic arterial disruption	0	1 (2%)	.8
Anastomotic artery pseudoaneurysm rupture	0	2 (3.9%)	.7
Portal thrombosis	0	4 (7.8%)	.5
Cava anastomotic leak	1 (9.1%)	1 (2%)	.3
Biliary leak	3 (27.3%)	10 (19.6%)	.4
Early biliary stricture	0	3 (5.9%)	.6
Delayed biliary stricture*	2 (13.3%)	13 (27.7%)	.5
Septic fluid collection	0	2 (3.9%)	.7
Retransplantation	0	5 (9.8%)	.5
Postoperative hospital death	1 (9.1%)	2 (3.9%)	.5
Acute renal failure	0	21 (42.9%)	.008

*Percentage among discharged patients.

A subgroup of 23 patients aged ≥60 years from group 2 were also studied to exclude a possible poorer outcome than in group 1. Again, no significant difference was found in the short-term morbidity variables.

Long-term Results

No group 1 patient showed clinical data (no jaundice), biochemical (normal AST, ALT, alkaline phosphatase, gamma-glutamyltranspeptidase) or radiologic (normal postoperative ultrasound and T-tube cholangiography), suggesting IC, with the exception of 2 cases (13.3%) with demonstrated stenosis limited to the bile duct anastomosis, yet without a significant difference, with 13 (27.7%) in group 2 (Table 1).

Only 1 case (10%) in group 1 and 3 (6.1%) in group 2 underwent delayed hepatic artery thrombosis, also without any significant difference.

Liver function has remained normal in group 1 patients after hospital discharge, for the follow-up period of study. One patient was diagnosed as having diffuse large B-cell lymphoma (germinal center type) 14 months after transplantation, with a good response to chemotherapy.

Estimated mean survival was 24.6 (95% CI, 20.2–29.1) months in group 1 and 32.3 (95% CI, 30.4–34.2) months, group 2, with no significant difference ($P = .7$).

DISCUSSION

In this study we have reported on a comparison between the results of liver transplantation in 2 different groups according to the type of donor: DCD or DBD. Both groups were comparable in terms of recipient features, such as age and MELD score, although donor age was lower in DCDs because age is a selection criterion by itself. Also, cold ischemia time was less in DCDs, reflecting that most of the procurement procedures were local by comparison, with 18 (35.3%) of the DBD procedures performed at other centers.

Our results for liver transplantation from DCDs using NRP with ECMO are quite good in terms of the nonincidence of IC and only 1 case of PNF. These findings, as well as the incidence of thrombosis and other hepatic artery complications, portal thrombosis, biliary anastomotic complications, or in-hospital postoperative death, were similar to DBD findings.

In one recent study, significantly more complications were observed in DCD patients with grafts retrieved with the super-rapid technique when compared with DBD liver transplants: IC, 11% vs 3%; PNF, 3% vs 1%; and retransplantation, 15% vs 5% [4]. The clinical consequences of IC are very harmful, with bouts of cholangitis and frequent need for biliary invasive procedures as well as retransplantation [3]. A meta-analysis of studies published between 1990 and 2008 comparing outcomes of liver transplants from DBD and controlled DCD showed IC rates of 3% and 16%, respectively [3]. Later studies reported IC rates of 8.5% [12], 12% [13], and 9.9% [14]. However, a recent series with controlled DCD reported a lower IC rate of 2.5%, with less clinical impact, as there was no need for retransplantation, and with both patient and graft survival comparable to that among patients receiving a donor liver after brain death [2].

Another crucial problem with DCD is the development of PNF, showing a 3.6-fold increased hazard compared with DBD [3].

NRP can decrease and even revert ischemic damage produced by hypotension after life support withdrawal and the interval period of 5 minutes after cardiac arrest required by the law. Also, both experimental [15] and clinical studies [16] have shown that NRP for 30 minutes can restore systemic mixed venous pH and mixed venous oxygen saturation (vSO_2) to near basal values in mixed venous blood. As a result, NRP can reduce hypoxemia duration as well as decrease graft ischemia hazard, especially of the biliary epithelium. Therefore, a decrease in PNF and IC rates can be expected.

Only a few case reports and case series of liver transplant from DCD using NRP have been published, indicating the

low incidence of IC. Studies with uncontrolled DCD reported IC rates of 5% [17] and 13% [5], as well as a 10% rate of PNF [17]. Concerning controlled DCD, Pelletier et al [18] reported 11 transplants with only 1 case (9%) of IC. Rojas-Peña et al [16] reported 13 transplants with 1 case (14.3%) of biliary stenosis and PNF. The most recent study indicated no cases of PNF or IC in a small series of 5 liver transplants [19]. Oniscu et al [20] reported 11 transplants, using NRP without cannulation or heparinization before life support withdrawal, with the resultant risk of microcirculation thrombosis, and found 4 cases of PNF (36.4%) and 1 death, but no IC. On the contrary, Butler et al [21], in a small series of 3 cases, also without cannulation or heparinization before life support withdrawal, observed no cases of IC or PNF. Other case reports have been published and showed no IC [7,22]. We observed no cases of IC after a minimum follow-up of 3 months, which is the interval typically used to assess its development [2].

Only 1 of our DCD cases developed PNF. Several predictors of PNF have been identified [14]: hepatitis C virus; liver tumors or body mass index >30 in the recipient; hepatitis B virus anti-core; and mean arterial pressure <60 mm Hg for >20 minutes after life support withdrawal in the donor or cold ischemia >6 hours. None of these factors were present in our patients. There was only 1 case of hepatic arterial thrombosis in the DCD patient group. This complication was reported in relation to the first experiences with DCD [23], although more recent reports have not confirmed a higher frequency compared with DBD [2–4,24].

Also, there were no cases of acute renal failure, a complication reported in 16.3% to 53.4% of controlled DCD cases (but without use of ECMO), compared with 4.1% to 31.8% in DBD patients [12,25]. Other authors also reported higher rates in DCD compared with DBD recipients, yet the latter showed acute renal failure ranging from 12% to 80%, depending on criteria used [26]. In our experience, significantly more DBD recipients, as high as 42.9%, developed acute renal failure. The reason for this is unclear because the functional status of the recipients, according to MELD score, postoperative treatment, or immunosuppression regimen, was not significantly different. In group 2 in our study, the cold ischemia time was longer, although this probably would not explain the difference sufficiently. Another influencing factor could be intraoperative hemodynamic instability, although the piggy-back technique used in all of our cases generally diminishes such instability [26]. Also, postreperfusion syndrome is a major factor in the onset of acute renal failure [26]; however, we have no explanation for its lower rate in DCD patients, although there is a possible protective effect with ECMO. Most studies concerning DCD donors were performed with the rapid recovery technique, yet several studies [8,16,20] showed that kidney grafts obtained using NRP with ECMO devices decreased the rates of delayed graft function in kidney recipients. We do believe that, as our initial experience, grafts were only accepted if the functional warm ischemic time was short, in most cases <30 minutes. This factor, combined with the potential protective effect of the ECMO device and the shorter cold ischemic time, could explain the low rate acute renal failure.

Primary sclerosing cholangitis was observed in 1 of our cases, but without long-term complications. Although the condition was previously considered a poor indicator for receiving a DCD liver, another recent study also reported excellent results in terms of graft and patient survival [27].

Because more advanced donor age is associated with poorer results, we also compared a subgroup of transplants from DBD patients >60 years old with the DCD patients, but the results were not significantly different in terms of PNF or vascular or biliary complications. As a result, we cannot support that the concept that DCD is better than DBD in older donors—although the age cut-off value is probably not very high. However, cut-off data for transplants at >60 of age are limited, so we more study is needed before we can draw conclusions.

A ethical barrier to the widespread acceptance of NRP in controlled DCD is the theoretical possibility of resuscitation of a patient after death declaration due to inadequate use of an aortic occlusion balloon [28]. However, a specific methodology to avoid restoring circulation to the brain after determination of death when using NRP and antemortem cannulation has been described recently [8] and validated in a multicenter study [29]. This proposal avoids the aforementioned ethical concern, guaranteeing the absence of cerebral resuscitation.

In conclusion, in our experience, the use of NRP with ECMO in the procurement of liver grafts from controlled DCD was associated with a minimal risk of PNF, IC, thrombotic complications, and acute renal failure, and not higher than in DBD transplants. However, the limitation of small patient numbers precludes any definitive conclusion, so greater patient numbers and longer follow-up times are needed in future studies. A possible protective effect of ECMO in preventing acute renal failure should also be investigated.

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