Donation After Cardiac Death in Liver Transplantation: An Additional Source of Organs With Similar Results to Donation After Brain Death

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ABSTRACT

Background. As new sources of organs are needed, liver transplantation using donors after cardiac death (DCD) is progressively increasing, but outcomes with this method are still questioned. This study was accomplished to verify that DCD outcomes are comparable to those seen in donation after brain death (DBD).

Methods. This was a prospective cohort study including 100 liver transplantation performed between 2014 and 2017, divided according to donor type in 75 DBD and 25 DCD.

Results. DCD donors were younger (mean age: DCD 56 years, DBD 59 years; $P = .009$). Mean Modified End-stage Liver Disease (MELD) score was lower for DCD (DCD 16, DBD 19; $P < .001$). No differences were found regarding ischemia times and development of postreperfusion syndrome or coagulopathy. Primary graft dysfunction was more frequent in DCD (60%, DCD 29.3%; $P = .006$). Rates of primary graft nonfunction (DCD 0%, DBD 1.3%; $P = .562$) and acute rejection (DCD 20%, DBD 16.4%; $P = .685$) were similar. Acute kidney injury occurred more often in DBD (DCD 32%, DBD 12%; $P = .051$). Length of stay was comparable. Rates of biliary complications (DCD 20%, DBD 26.7%; $P = .505$) were similar, unlike ischemic cholangiopathy (DCD 12%, DBD 1.3%; $P = .018$). Retransplantation rates were also similar (DCD 8%, DBD 4%; $P = .427$) as was survival rate after 3 years (DCD 84%, DBD 86.7%; $P = .739$).

Conclusion. DCD represents an additional graft source with results that are encouraging and may be comparable to DBD with a careful donor and recipient selection.

SPAIN has been long a world leader among nations with regard to organ donation and transplantation. In 2016, there were 43.4 registered deceased donors per million population (pmp) and 24.9 liver transplants pmp [1], with a total of 1159 liver transplants. However, these impressive numbers are not sufficient to cover the existing demand. According to data provided by the National Organization of Transplantation (ONT) on liver transplantation in adults, at the beginning of 2016 there were 759 patients on the waiting list. Later that year 1258 additional patients were included and the performed transplants, the deaths and the exclusions the number of patients in the waiting list at the end of the year was still quite high (616 patients) [2]. Therefore, there is an increasing need to extend donation acceptability criteria and identify new organ sources. One of these new sources is donation after cardiac or circulatory death (DCD). In our country there has been remarkable growth in DCD frequency after the law regulating controlled DCD (Maastricht type III) was approved in 2012 [3]. Thus, last year, Spain was the country with the largest number of DCD procedures worldwide: 10.6 donors pmp [1]. At our hospital, the DCD program was established in 2014. Since then up to

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15% of liver transplants have come from this donor group on a yearly basis. DCD has shown comparable postoperative and long-term results to donation after brain death (DBD) in liver transplantation [4], provided that adequate selection of donors and recipients is undertaken. Nevertheless, there are certain complications that have been directly related to this kind of donation, such as ischemic biliary complications. Thus, the impact of these drawbacks on patient and graft survival must be taken into account [5].

MATERIALS AND METHODS

The aim of our study was to compare postoperative and medium-term results between recipients of liver transplantation from DBD and from controlled DCD (Maastricht type III).

This prospective, cohort-based study, performed between March 2014 and May 2017, consisted of 100 adult liver transplantations divided into 2 groups: a DBD group (n = 75) and a DCD group (n = 25). Groups were chosen randomly (DBD controls were the 2 transplantations made before the DCD one and the one made after it). Exclusion criteria were acute hepatic failure and emergent and multivisceral transplantation. We analyzed demographic variables of the donor and recipient, Modified End-stage Liver Disease (MELD) score, Child-Pugh classification, etiology of liver disease, ischemia time, intraoperative events (postreperfusion syndrome, coagulopathy, need of hemoderivatives), functionality (primary graft dysfunction and nonfunction), acute cellular rejection, length of stay, readmissions, postoperative complications, long-term complications, biliary complications, retransplantation, and mortality.

In controlled DCD, the protocols from the ONT [6] and our hospital were followed: the maximum established donor age was 65 years, and the functional warm ischemia time had to be <30 minutes. Limitations regarding therapeutic effort were made in the operation room after family consent. The super-rapid technique for organ extraction was used in 21 cases and normothermic regional perfusion with extracorporeal membrane oxygenation (ECMO) in 4 cases. The preservation solution used was histidine-tryptophan-ketoglutarate (HTK) in all cases. Regarding the surgical technique, we usually construct a temporal portocaval shunt, with "piggy-back" during the explant, and biliary reconstruction with choledocho-choledochostomy without regular use of Kehr tutor. There were no differences in immunosuppression based on donor types, as we usually establish induction with corticosteroids and an anticalcineuric agent, adding the latest immediately or delayed depending on the risk of developing acute kidney injury (employing then initially basiliximab [7]).

Statistical analysis was made using SPSS version 22 for Windows (IBM SPSS, Armonk, NY, United States), with the typically used statistical tests, depending on the variables. $P < .05$ was considered significant.

RESULTS

Donors

The mean age of DCD donors was lower than that of DBD donors (DCD 52 years, DBD 59 years), which is self-explanatory due to the age limit established in the DCD protocol (Table 1). Moreover, statistically significant differences were found in greater use of vasoactive drugs for DBD and a longer stay in the intensive care unit for DCD. Reasons for death among the donors were heterogeneous—even though the predominating cause was stroke, there was an increased presence of anoxic encephalopathy in DCD.

Recipients

The liver diseases motivating transplantation were similar in the 2 groups, with hepatocellular carcinoma (HCC) the leading indication in our series. Transplantation groups in our region use MELD score for organ allocation [8] and, accordingly, end-stage liver disease seemed to be more severe in the DBD group, given that average MELD was higher (19 in DBD and 16 in DCD). Moreover 44% of the patients were Child-Pugh class C.

Intraoperative Time

Standards for ischemia times established by our protocols [6] were attained. In our DCD cases, the average functional warm ischemia time was 16 minutes and the average total warm ischemia time was 24 minutes. Cold ischemia time was slightly shorter in DCD. No disparity was shown in development of postreperfusion syndrome, coagulopathy, or fibrinolysis. An increased need for red blood cell concentrates was seen in DBD recipients.

Postoperative Time

Regarding functionality, primary graft dysfunction (PGD, defined by the Olthoff criteria [9]) was markedly more frequent in DCD recipients (odds ratio [OR], 3.61; 95% confidence interval [CI], 1.40–9.27); however, no differences were seen in terms of primary graft nonfunction or length of hospital stay (Table 2). Moreover, similar numbers of DCD recipients with PGD lost their grafts (6.7%) than DCD recipients with no PGD (10%) ($P = .763$). In addition, the rate of complications was similar in the 2 cohorts, as well as the number of severe complications (Clavien ≥III), reinterventions, and cases of acute cellular rejection. No increase in acute kidney injury (AKI) or need for replacement therapy was observed in DCD.

Follow-up

A similar rate of retransplantation was found between the cohorts in our sample. Among the DCD recipients, 1 retransplantation was performed on the first postoperative day due to hyperacute rejection and another was made 2 months later, as indicated for ischemic cholangiopathy. On the other hand, among DBD recipients, 1 early retransplantation was needed due to primary graft nonfunction and 2 were done later due to ischemic cholangiopathy and chronic rejection, respectively.

Survival analysis after up to 3 years (Fig 1) showed comparable Kaplan-Meier curves for the 2 groups (DCD 84%, DBD 86.7%; $P = .572$), with similar average survival (DCD 1037 days, DBD 1097 days). Various causes of death were seen in the DCD cohort. In the immediate postoperative period, 2 patients died: 1 due to sudden death with an inconclusive autopsy and another due to hyperacute

Table 1. Characteristics of Donors and Recipients: Intraoperative Variables

Variable	DCD	DBD	*P* Value
Number	25	75	
Donor age (years)	52 (22–65)	59 (28–84)	.009
Donor sex (male/female)	19 (76%)/6 (24%)	44 (58.7%)/31 (41.3%)	.120
Donor BMI	26.49	27.38	.306
Donor ICU stay (days)	8.32	2.92	<.001
Use of vasoactive drugs	36%	82.4%	<.001
Donor cause of death			<.001
Stroke	13 (52%)	57 (76%)	
Brain trauma	2 (8%)	13 (17.3%)	
Anoxic encephalopathy	10 (40%)	5 (6.7%)	
Recipient age, years old	57 (45–69)	57 (27–69)	.858
Recipient sex (male/female)	20 (80%)/5 (20%)	57 (76%)/18 (24%)	.681
Recipient BMI	26.69	27.08	.702
MELD score	16 (15–25)	19 (15–30)	<.001
Child-Pugh (class C)	4 (16%)	33 (44%)	.012
Etiology of liver failure			.739
Viral	5 (20%)	22 (29.3%)	
Alcoholic	8 (32%)	17 (22.7%)	
Hepatocellular carcinoma	8 (32%)	24 (32%)	
Others	4 (16%)	12 (16%)	
Total warm ischemia time (min)	24 (12–38)		
Functional warm ischemia time (min)	16 (10–23)		
Cold ischemia time, min	277	318	.058
Warm ischemia time (implant) (min)	50	50	.954
Postreperfusion syndrome	6 (24%)	9 (12%)	.146
Coagulopathy	2 (8%)	13 (17.3%)	.258
Fibrinolysis	2 (8%)	11 (14.7%)	.391
Need of hemoderivatives			
Red cell concentrates (mL)	276	593	.026
Platelets (mL)	130	182	.469
Plasma (mL)	275	498	.087

Abbreviations: BMI, body mass index; ICU, intensive care unit; MELD, Modified End-stage Liver Disease.

rejection that relapsed after retransplantation. During follow-up, 2 more patients died: 1 as a result of chronic rejection and the other due to severe pancreatitis after endoscopic retrograde cholangiopancreatography (ERCP) upon diagnosis of ischemic cholangiopathy 3 years post-transplant. Thus, there was only 1 death attributable to type of donor.

Biliary Complications

Global, early (defined as those in the first 3 months), and late (defined as those after 3 months) biliary complication rates were comparable between groups. After endoscopic, percutaneous, or surgical treatment, 76% of these complications were eventually resolved.

During the postoperative period, 4 biliary fistulas were observed in the DBD group, all treated endoscopically/percutaneously. On the other hand, 1 DCD patient developed a postoperative biliary fistula that required reintervention and eventually needed a hepatojejunostomy. Anastomotic stricture was more typically found in the late period.

Ischemic cholangiopathy (IC) was seen in 3 DCD recipients and 1 DBD recipient. Calculated ORs show that the risk of developing this complication was 10 times higher in DCD. The DBD IC case was secondary to postoperative arterial thrombosis (treated initially with angioplasty), requiring retransplantation after 2 months. One DCD case arose 3 months after transplant, with anastomotic stricture and biliary tract necrosis that required a hepatojejunostomy and, ultimately, retransplantation. A second case was identified 2 years after transplant and was treated with percutaneous transhepatic cholangiography (PTHC), with several percutaneous balloon dilations and subsequent removal of internal-external drainage. The patient is currently asymptomatic. The third case was diagnosed after 3 years, with ERCP performed due to a suspected biliary stricture. Unfortunately, the patient died after complications related to the procedure.

DISCUSSION

Based on current protocols [6], DCD has shown similar demographic characteristics to DBD (except for the already known age limit, which may eventually be expanded [10]).

According to the existing evidence, DCD recipients should be carefully selected to accomplish good results.

Table 2. Postoperative and Follow-up Results

Variable	DCD	DBD	*P* Value
Number	25	75	
ICU stay (days)	3.88 (2–12)	5.09 (1–25)	.223
Surgery ward stay (days)	11.08 (0–43)	11.05 (0–45)	.940
Readmission	0	16 (21.3%)	.012
Peak GOT (U/L)	5255	1651	.024
Peak GPT (U/L)	2131	1046	.017
Primary graft dysfunction	15 (60%)	22 (29.3%)	.006
Primary graft nonfunction	0	1 (1.3%)	.562
Postoperative complications	16 (64%)	47 (62.7%)	.905
Severe complications (Clavien $\geq$ III)	7 (28%)	23 (30.7%)	.930
Reinterventions	3 (12%)	8 (10.7%)	.854
Acute cellular rejection	5 (20%)	12 (16.4%)	.685
Acute kidney injury	3 (12%)	24 (32%)	.051
Need for replacement therapy	1 (33%)	10 (41.7%)	.782
Biliary complications	5 (20%)	20 (26.7%)	.505
Early onset biliary complications	3 (12%)	11 (14.7%)	.739
Biliary fistula	1	4	
Anastomotic stricture	1	6	
Ischemic cholangiopathy	1	1	
Late-onset biliary complications	2 (8%)	9 (12%)	.798
Anastomotic stricture	0	9	
Ischemic cholangiopathy	2	0	
Ischemic cholangiopathy	3 (12%)	1 (1.3%)	.018
Retransplantation	2 (8%)	3 (4%)	.427
Early	1 (4%)	1 (1.3%)	.409
Late	1 (4%)	2 (2.7%)	.744
Mortality	4 (16%)	10 (13.3%)	.739
Postoperative mortality	2 (8%)	3 (4%)	
Global survival, days	1037 (2–1243)	1097 (3–1265)	.652

Abbreviations: GOT, glutamate-oxaloacetate transaminase; GPT, glutamate-piruvate transaminase; ICU, intensive care unit.

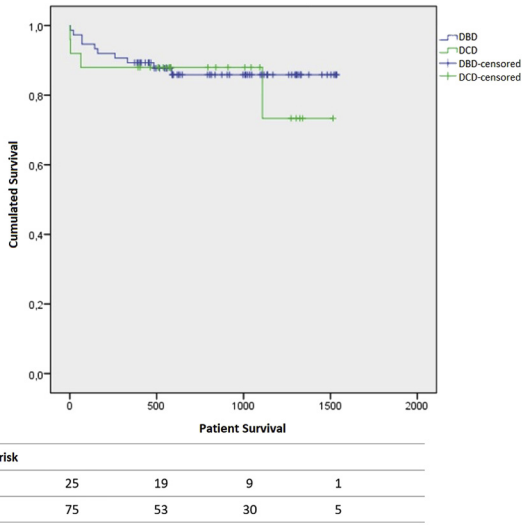

Fig 1. Kaplan-Meier curves for global patient survival.

There is controversy as to whether this kind of organ, somehow considered of "lower quality," should be given to sick or relatively fit patients [11]. It has been suggested that those with higher MELD or HCC without MELD exception points are the ones who actually benefit in terms of survival from DCD [12]; on the other hand, healthier recipients may balance the so-called worse quality in terms of better tolerance to future complications. Moreover, some groups have advised cautious use of DCD in recipients with hepatitis C because they may experience an increased rate of recurrence and ulterior graft failure [13]. A subsequent meta-analysis showed no differences except for an increased risk of primary nonfunction [14], and although further studies are needed we find no strong evidence to avoid this kind of recipients with DCD. In our experience, proper matching of DCD with recipient should include avoiding recipients with extreme MELD scores or previous kidney failure.

Longer ischemia times are known to increase the risk of complications arising from ischemia/reperfusion injury, especially biliary complications [15], so there is a high-priority need to shorten these times in DCD, as in our series. In addition, DCD organs did not cause variations in the anesthetic management of recipients during the operation.

Furthermore, greater peak transaminases were reached in DCD, and this resulted in a significant increase in PGD, as described in previous series [16]; nevertheless, in our sample, this had no impact on primary graft nonfunction or graft and recipient survival. This finding suggests that the Olthoff criteria may not be the best predictor of functionality for this kind of organ [17].

In addition AKI has been described to develop more often in recipients from DCD, with a more frequent need for renal replacement therapy [18]. Its pathogenesis seems to be multifactorial but may be related to ischemia/reperfusion injury, and increasing peak transaminases may be the only predictor. Nevertheless, this rise of AKI was not observed in our series.

IC is the main complication related to DCD. Its incidence varies from 8% to 38% in different series (average 16%) [5]. IC is a diffuse nonanastomotic biliary stricture secondary to ischemia/reperfusion injury, which affects not only quality of life (because of the need for multiple hospital admissions and invasive procedures) but also graft and patient survival

[19]. In our series the rate was slightly lower than the published average, and we found it remarkable that 2 of our 3 cases had a late onset (>2 years after transplantation), which raises questions of whether there is a real relationship between this kind of donor and the development of IC. The greatest challenge in DCD is to find strategies that decrease or avoid this devastating complication [20]. The best evidence has focused on restrictive donor selection criteria, limiting then known risk factors such as cold ischemia time to >8−10 hours, warm ischemia time to >30 minutes, and age to >60−65 years (although age on its own is a debatable criteria nowadays). Moreover, preliminary experiences have shown that normothermic regional perfusion (NRP) may decrease IC [21] as this could limit and restore ischemic damage, although further studies are needed. Accordingly, we must point out that, in our limited experience, our 4 DCD cases with NRP did not develop IC. Profit from the use of high-viscosity preservation solutions and fibrinolytic agents remains controversial.

Finally, graft loss and mortality have been initially described at greater frequency in DCD liver recipients [22], but this was not the case in our series. Again, making proper donor and recipient selection and avoiding other well-established risk factors is enough to grant similar graft and patient survival rates [23,24].

CONCLUSION

DCD is a useful additional source of liver grafts. With careful selection of donors and recipients overall outcomes may be comparable to those seen with DBD. The main complication associated with DCD is IC, which may be mitigated through use of NRP.

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