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Applicability and Results of Maastricht Type 2 Donation After Cardiac Death Liver Transplantation

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Maastricht type 2 donation after cardiac death (DCD) donors suffer sudden and unexpected cardiac arrest, typically outside the hospital; they have significant potential to expand the donor pool. Herein, we analyze the results of transplanted livers and all potential donors treated under our type 2 DCD protocol. Cardiac arrest was witnessed; potential donors arrived at the hospital after attempts at resuscitation had failed. Death was declared based on the absence of cardiorespiratory activity during a 5-min no-touch period. Femoral vessels were cannulated to establish normothermic extracorporeal membrane oxygenation, which was maintained until organ recovery. From April 2002 to December 2010, there were 400 potential donors; 34 liver transplants were performed (9%). Among recipients, median age, model for end-stage liver disease and cold and reperfusion warm ischemic times were 55 years (49–60), 19 (14–21) and 380 (325–430) and 30 min (26–35), respectively. Overall, 236 (59%) and 130 (32%) livers were turned down due to absolute and relative contraindications to donate, respectively. One-year recipient and graft survivals were 82% and 70%, respectively (median follow-up 24 months). The applicability of type 2 DCD liver transplant was <10%; however, with better preservation technology and expanded transplant criteria, we may be able to improve this figure significantly.

Key words: Donation after cardiac death, extracorporeal membrane oxygenation, ischemic cholangiopathy, liver transplant

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CPR, cardiopulmonary resuscitation; CRS, cardiorespiratory support; CTP, Child-Turcotte-Pugh; CVA, cerebrovascular accident; DBD, donation after brain death; DCD, donation after cardiac death; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IC, ischemic cholangiopathy; ICU, intensive care unit; IOM, Institute of Medicine; LD, live donation; MI, myocardial infarction; MELD, model for end-stage liver diseae; NECMO, normothermic extracorporeal membrane oxygenation; NMP, normothermic machine perfusion; PEI, percutaneous ethanol injection; OLT, orthotopic liver transplant; UAGA, Uniform Anatomical Gift Act.

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Introduction

Based on an expanding need for organs for transplant and the fact that the "ideal donor" (<45 years, brain dead after trauma or motor vehicle accident) is less frequent, the use of organs from alternative sources is increasingly more common. Even in Spain, a country with a high rate of donation, demand for transplantable organs surpasses the supply (1). Transplant centers here have turned to live donation (LD) and donation after cardiac death (DCD) donors to better meet their waiting-list needs.

DCD donors are classified among four categories according to the Maastricht criteria (2). In Maastricht type 1, death is declared at an extrahospitalary site and the potential donor is brought to the hospital without resuscitation attempts. In type 2, arrest occurs unexpectedly; resuscitation attempts are made but are unsuccessful. In type 3, cardiac arrest is induced by removing ventilatory support from a patient with brain damage insufficient to declare brain death. Finally, in type 4, brain death is declared before unanticipated cardiac arrest. Types 1, 2 and 4 are considered uncontrolled and type 3 controlled.

DCD has garnered significant interest recently. In the United States, although the organ procurement rate from deceased donors has decreased, the number of DCD donors has increased progressively over the past decade. In 2008, 10.6% of US organ donors were categorized as DCD (3). This trend is due to policies set forth by prominent healthcare organizations, such as the Joint Commission on Accreditation of Healthcare Organizations (4), United Network for Organ Sharing (5), United States Department of Health and Human Services Organ Donation Breakthrough

Collaborative (6) and United States Institute of Medicine (IOM; Ref. 7), all intended to increase DCD.

In 2006, the IOM recommended the transplant community undertake active efforts to increase donation from Maastricht type 2 DCD donors in particular, estimating that this group could expand the donor pool by 22 000 per year (7). However, clinical experience with the use of uncontrolled DCD livers is limited. An early article from the University of Pittsburgh included six liver transplants performed using Maastricht type 4 DCD donors that arrested after or during the declaration of brain death (8). The results were poor: only one graft survived beyond 2 months. The group from La Coruña, Spain, has submitted two reports detailing 27 type 2 DCD liver transplants, though the donors were maintained according to heterogeneous methods: simultaneous chest and abdominal compressions or hypothermic or normothermic extracorporeal membrane oxygenation (NECMO; Ref. 9,10). Finally, a report from Madrid, Spain, described the results of 20 type 2 DCD liver transplants, although the mean follow-up was too short (10.8 ± 7.4 months, median follow-up not mentioned) to appropriately evaluate the development of ischemic cholangiopathy (IC), a significant cause of failure among DCD livers (11).

In 2002, we implemented a clinical protocol to maintain and recover Maastricht type 2 DCD livers (12). Currently, we have one of the most active type 2 DCD liver transplant programs worldwide. Nonetheless, we have observed that, despite its potential, the clinical applicability of this form of transplant is low. In this updated study, we analyze not only the results of livers used for transplant but all potential donors treated under our protocol, to determine causes for rejection for transplant and means of improving their yield.

Patients and Methods

Our type 2 DCD liver transplant protocol was described previously (12); since then, it has been modified slightly.

Phase I: Advanced cardiorespiratory support (CRS)

Cardiac arrest is witnessed. Emergency medical services are mobilized to the scene, initiate advanced life support and transfer the patient to the hospital. If at least 20 min of ongoing asystole pass without a reversible cause, the arrest may be considered irreversible and further attempts at resuscitation futile (13). If the patient fulfills basic type 2 DCD donor criteria (≤65 years, no criminality or violent death), transplant coordinators are notified about the pending arrival of the potential donor, thereby activating the protocol. The potential donor is then placed on a LUCAS chest compression system (Jolife AB, Lund, Sweden).

At the hospital, chest compressions are withheld so that death may be diagnosed based on the absence of cardiac function and spontaneous respiration during a no-touch period of ≥5 min (14). After the death declaration, transplant coordinators have their first contact with the potential donor. The endotracheal tube is connected to a ventilator and LUCAS^{TM} restarted. Blood samples are taken, heparin is administered (3 mg/kg i.v.) and the surgical team is called.

Through an infrainguinal incision, the femoral artery and vein are cannulated with 14–21 Fr and 22–26 Fr perfusion catheters, respectively (Maquet Gmbh & Co. KG, Rastatt, Germany). The venous catheter is advanced far enough to terminate at the estimated level of the diaphragm/hepatic veins. The catheters are filled retrograde with donor blood, clamped distally and connected to the tubing of a NECMO circuit. In series, the NECMO circuit consists in a reservoir, a pump and an oxygenator connected to a heater and an oxygen source (12). It is primed with 500 mL 1/6 M sodium bicarbonate, 500 mL 10% mannitol, 500 mL Plasmalyte and 500 mL Voluven (Fresenius Kabi, Bad Homburg, Germany).

Phase II: Normothermic extracorporeal membrane oxygenation

Through a contralateral infrainguinal incision, the opposite femoral artery is cannulated with a Fogarty balloon catheter (Edwards Lifesciences LLC, Irvine, CA, USA), which is advanced into the supraceliac aorta. The balloon is inflated with contrast as clamps are removed from the perfusion catheters, and NECMO is begun. Proper positioning of the balloon immediately above the diaphragm and the venous catheter immediately below it is confirmed by chest radiograph. Blood is sampled at baseline and throughout NECMO to determine biochemical and hematological parameters and acid–base status. Pump flow is maintained >1.7 L/min, temperature 35.5–37.5°C and pH 7.0–7.4. Additional heparin (1.5 mg/kg i.v.) is given every 90 min.

Phase III: Organ recovery

NECMO is continued until cold perfusion at organ recovery, unless the potential donor is deemed ineligible before that point. At organ recovery, the abdomen is thoroughly explored. The choledochus is cut distally to judge its vascularity. The gall bladder is also cut at its fundus, and an antegrade flush through the choledochus is performed. Only cannulation of the portal vein is necessary because the aorta is perfused through the femoral artery. A rapid-flush technique is used to perfuse the liver and the kidneys. Before mid 2010, we used University of Wisconsin solution (2 L portally, 4 L arterially); since then, we use Celsior (Genzyme, Naarden, The Netherlands), based on a policy change at our hospital (3 L portally, 5 L arterially). The remainder of the dissection and organ extraction is performed in hypothermia. On the backtable, a high-pressure flush of the hepatic artery is performed using 20–30 mL of preservation solution.

For livers ultimately deemed suitable, transplantation is performed in the first recipient on the transplant waiting list, which, at our center, is organized according to blood type and model for end-stage liver disease (MELD) score. The recipient's inferior vena cava is preserved, and the biliary anastomosis is performed over a T-tube, through which cholangiography is performed to evaluate the biliary tree at 3 months or sooner, depending on the patient's clinical course. The diagnosis of IC is made when there are diffuse intrahepatic strictures on biliary imaging, without concomitant hepatic artery thrombosis (15).

Donor evaluation and contraindications to donate

After death has been declared and the cannulation process initiated, the potential donor's next-of-kin is contacted for information and consent. Absolute contraindications include a history of alcohol abuse or liver disease; biological risk factors, including intravenous drug abuse; cancer; hepatitis B virus, hepatitis C virus or HIV infection and criminality or violent death. Trauma to the abdominal or femoral vasculature preventing the use of NECMO also precludes donation.

Other contraindications to donate are based on the donor's evolution (12). When the protocol was designed, time limits were set for each phase: <15 min of cardiac arrest without cardiopulmonary resuscitation (CPR), <150 min of CRS and <4 h of NECMO. A potential donor that exceeds any one

of these is considered ineligible. For liver donors, hepatic transaminases at the start of and during NECMO have to be less than roughly three and four times the upper limit of normal, respectively. Finally, at organ recovery, the liver, gall bladder and choledochus have to have an adequate macroscopic appearance. If the liver appears congested, poorly perfused, steatotic or fibrotic, it is rejected. Also, if the sectioned choledochus appears poorly vascularized, the graft is not used. Wedge hepatic biopsies are taken before cold perfusion for academic and research purposes but they are not used in the decision to transplant the graft.

Data and statistical analysis

Data regarding protocol activations and type 2 DCD transplants performed between April 2002 and December 2010 was collected, as was survival data for donation after brain death (DBD) transplants performed during this period. Continuous variables are presented as the median and 25–75% interquartile range. Parametric and nonparametric variables were compared using Student's t and Mann–Whitney U tests, respectively. Qualitative variables were analyzed using Pearson's chi-square test. Survival was analyzed according to the method of Kaplan–Meier and comparisons between groups made using the Mantel–Cox log-rank test. $p < 0.05$ was significant. Statistical analysis was performed using Predictive Analytics SoftWare Statistics version 18.0 (IBM, Somers, NY, USA).

Institutional and recipient approval

This protocol was approved by the Hospital Clínic Institutional Ethics Committee (1998/210). Patients listed for liver transplant at our center are informed of the possibility of receiving a DCD liver and sign their consent.

Results

Figure 1 depicts the results of the 400 activations of the Hospital Clínic type 2 DCD protocol. Of the potential donors that were ultimately excluded, roughly one-third were excluded before cannulation, one-third after cannulation and one-third in the operating room at organ recovery. Figure 2 shows the year-to-year evolution of type 2 DCD activity at our center. Overall, activity increased every year except for one (2006), and a total of 34 liver transplants were performed: 11 in the first 5 years of the program and 23 in the last 4 years.

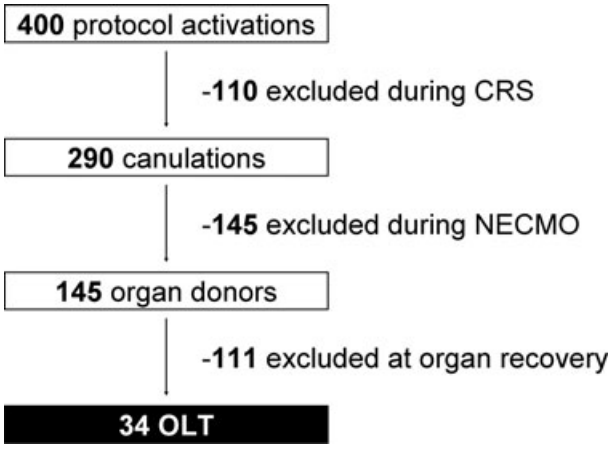


Figure 1: Results of 400 activations of the Hospital Clínic type 2 DCD liver transplant protocol. Overall, 34 liver transplants were performed. CRS = cardiorespiratory support; NECMO = normothermic extracorporeal membrane oxygenation; OLT = orthotopic liver transplantation.

Reasons for rejecting a potential type 2 DCD donor

Among potential type 2 DCD donors, 366 were deemed ineligible. Table 1 depicts contraindications for transplant. Overall, the most common was inadequate venous return during NECMO, followed by prolongation of a phase of the protocol and elevation of hepatic transaminases above predefined limits.

Reasons for rejection were grouped according to five categories: donor contraindication, refusal of consent, technical or logistical failure, suboptimal evolution and other (Figure 3). Donor contraindications included a history of alcohol or liver disease, biological risk factors or cancer; infectious disease and peritonitis. Refusal of consent included refusals made by the family or a judge. Technical or logistical failures included inadequate venous return during NECMO; vascular trauma preventing the use of NECMO; logistical reasons, such as no recipient of the same blood type; inadequate oxygenation before NECMO and pump failure. Suboptimal evolution was based on transaminases during NECMO or the length of a phase that exceeded protocol limits or poor macroscopic aspect of the liver at recovery. Other reasons did not fit into the aforementioned categories and applied to less than 1% of cases.

Organ donors

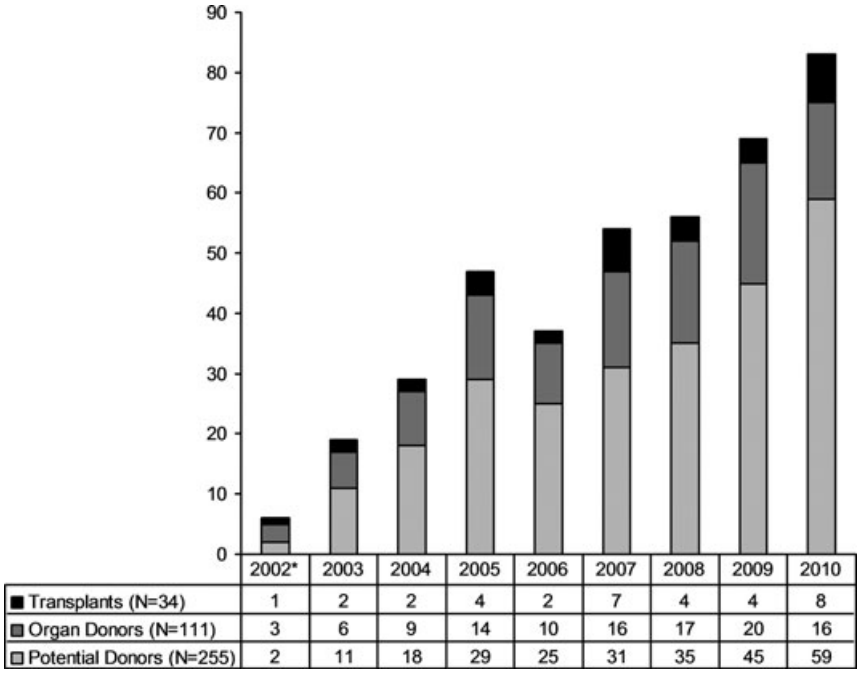
Among 145 type 2 DCD organ donors (Figure 1), median age and BMI were 51 years (42–59 years) and 26.1 (24.2–29.3), respectively; 123 (85%) were men. The most common causes of death were myocardial infarction (N = 73, 50%) and arrhythmia (N = 29, 20%). Donation outcomes were as follows: 30 (21%), two kidneys and liver; 2 (1.4%), one kidney and liver; 58 (40%), two kidneys; 9 (6%), one kidney; 2 (1.4%), liver and 44 (30%), no organs valid for transplant.

Table 2 compares characteristics of organ donors whose livers were and were not used for transplant. Overall, liver donors were younger and had lower BMIs and lower hepatic transaminases. A greater percentage had a history of arrhythmia.

Liver transplants

Thirty-four transplants were performed using type 2 DCD livers. Table 3 depicts recipient characteristics. Cold ischemic and reperfusion warm ischemic times were 380 (325–430) and 30 (26–35) min, respectively. University of Wisconsin was the preservation solution used in the first 28 transplants and Celsior in the last 6 transplants.

All DCD liver recipients were followed for at least 6 months posttransplant, unless they died sooner. With median



	2002*	2003	2004	2005	2006	2007	2008	2009	2010
Transplants (N=34)	1	2	2	4	2	7	4	4	8
Organ Donors (N=111)	3	6	9	14	10	16	17	20	16
Potential Donors (N=255)	2	11	18	29	25	31	35	45	59

Figure 2: Year-to-year evolution of type 2 DCD activity at our center. Organ donors are type 2 DCD donors that made it to the organ recovery phase of the protocol whereas potential donors are those that were excluded before the operating room. Overall, 34 liver transplants were performed. *April–December 2002.

follow-up of 24 months (range 0–111), 1-year patient and graft survivals were 82% and 70%, respectively.

To determine changes in the series over time, the first half of the series (first 17 recipients) was compared with the second. Among the first half, 12 recipients (71%) were Child-Turcotte-Pugh (CTP) class C preoperatively, whereas only 6 (35%) were CTP C among the second ($p = 0.039$). Similarly, the pretransplant MELD score tended to be higher among the first half versus the second: 20 (18–23) versus 16 (14–19; $p = 0.112$). Furthermore, 9 recipients (53%) among the first half and 3 (18%) among the second were admitted to the hospital preoperatively with hepatic decompensation ($p = 0.031$). In terms of outcome, the number of grafts surviving 6 months after transplant was significantly higher among the second half of the series, 15 (88%), versus the first, 9 (53%) ($p = 0.024$).

Table 1: Summary of contraindications to donate for 400 potential type 2 DCD donors

	N (%)
Inadequate venous return	72 (18%)
Phase prolonged	49 (12%)
Elevated AST/ALT	47 (12%)
Family refusal	40 (10%)
Poor macroscopic aspect	34 (8.5%)
History of alcohol or liver disease	29 (7.3%)
Judicial refusal	26 (6.5%)
Biological risk	21 (5.3%)
Vascular trauma	12 (3.0%)
Cancer	10 (2.5%)
Infectious disease	10 (2.5%)
Logistical	7 (1.8%)
Inability to oxygenate	4 (1.0%)
Peritonitis	2 (0.5%)
Pump failure	1 (0.3%)
Other	2 (0.5%)
No contraindication	34 (8.5%)

Biliary complications

Biliary complications occurred in four recipients (12%). There were three cases of IC (8%), evident 1, 2 and 3 months posttransplant, who underwent retransplantation at 8, 5 and 13 months, respectively. Characteristic features of IC, including ischemic bile duct necrosis, peribiliary inflammation, periductal fibrosis and/or biliary casts (16), were present on explant pathology. A fourth patient developed an anastomotic biliary stricture and successfully underwent hepaticojejunostomy at 58 months.

Overall liver transplant activity

Between April 2002 and December 2010, 626 DBD, 57 adult-to-adult LD, 34 domino and 4 adult-to-adult split liver transplants were performed, and a total of 819 livers from DBD donors were evaluated intraoperatively by our center. The applicability of DBD liver transplant was 76%.

Excluding retransplants and multiorgan transplants, 538 primary DBD liver transplants were performed. Median follow-up was 44 months and 1-year patient and graft survivals were 90% and 87%, respectively. Graft survival was significantly higher for the recipients of DBD versus DCD livers ($p = 0.011$), although patient survival did not vary ($p = 0.141$; Figure 4).

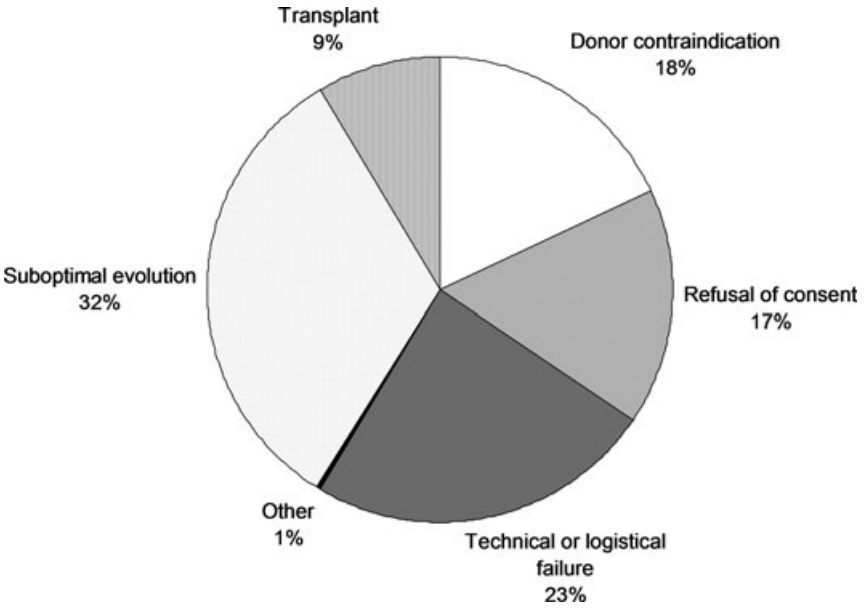


Figure 3: Outcomes of potential type 2 DCD liver donors. Contraindications to donate were grouped according to one of five categories. Suboptimal evolution, the only category that included relative contraindications to donate, represented the greatest proportion. If we were able to use more livers from potential donors in this category, we could increase the applicability of type 2 DCD liver transplantation from 9% to as high as 41%.

Discussion

This is the largest series of type 2 DCD liver transplants published to date. In our setting, the applicability of the procedure, based on protocol activations, was <10%, less than the 76% rate observed among DBD livers. One needs to consider, however, that livers from DBD donors with absolute contraindications (refusal of consent, alcohol or liver disease, biological risks, cancer or infectious disease) were never seen by our team. Furthermore, although it might not

Table 2: Comparison between type 2 DCD organ donors whose livers were and were not used for transplant

	Liver donor (N = 34)	Non liver donor (N = 111)	p-Value
Age (years)	47 (27–56)	51 (44–59)	0.02
Male (%)	28 (82%)	95 (86%)	NS
BMI	24.6 (23.1–26.2)	27.1 (24.7–30.9)	<0.001
Cause of death (%)			NS
Acute MI	16 (47%)	57 (51%)	–
Arrhythmia	10 (29%)	19 (17%)	–
Trauma	5 (15%)	9 (8%)	–
CVA	1 (3%)	8 (7%)	–
Other	2 (6%)	18 (17%)	–
Medical antecedents (%)			
Arrhythmia	6 (18%)	6 (5%)	0.02
Structural heart disease	7 (21%)	29 (26%)	NS
Diabetes mellitus	1 (3%)	6 (5%)	NS
Hypertension	7 (21%)	20 (18%)	NS
Hyperlipidemia	8 (24%)	15 (14%)	NS
Tobacco	11 (32%)	33 (30%)	NS
Cardiac arrest (min)[1]	7 (5–10)	6 (1 – 10)	NS
CRS (min)	112 (103–135)	122 (102–141)	NS
NECMO (min)	198 (183–225)	205 (178–240)	NS
AST_0 (IU/L)	52 (39–92)	95 (57–196)	0.002
ALT_0 (IU/L)	52 (30–86)	103 (47–229)	0.001
AST_{Final} (IU/L)	184 (116–247)	288 (160–700)	<0.001
ALT_{Final} (IU/L)	149 (70–209)	292 (130–636)	<0.001

Other causes of death included acute respiratory insufficiency, aortic aneurysm or dissection, pulmonary embolism, septic shock or systemic inflammatory response syndrome and upper gastrointestinal bleed. The "0" and "Final" subscripts denote baseline and final values, respectively. CRS = cardio respiratory support; CVA = cerebrovascular accident; MI = myocardial infarction; NECMO = normothermic extracorporeal membrane oxygenation.

[1]Cardiac arrest refers to initial period of cardiac arrest, before the initiation of cardiopulmonary resuscitation; it does not include the 5-min no-touch period.

Table 3: Pretransplant characteristics of recipients of type 2 DCD livers

	Recipients (N = 34)
Age (years)	55 (49–60)
Male (%)	21 (62%)
MELD	19 (14–21)
BMI	25 (23–28)
Underlying liver disease (%)[1]	
Alcoholic cirrhosis	8 (24%)
Autoimmune hepatitis	1 (3%)
Cryptogenic cirrhosis	1 (3%)
HBV infection/cirrhosis	4 (12%)
HCC	11 (32%)
HCV cirrhosis	25 (74%)
Primary biliary cirrhosis	1 (3%)
Subacute hepatic failure	1 (3%)
Child-Turcotte-Pugh class (%)	
A	7 (21%)
B	9 (26%)
C	18 (53%)
Cause of admission (%)	
Elective	21 (62%)
Hepatic decompensation	12 (35%)
PEI	1 (3%)

BMI = body mass index; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; MELD = model for end-stage liver disease; PEI = percutaneous ethanol injection.
[1]Some patients had more than one diagnosis.

seem cost-effective to maintain such a program based on its apparently low applicability, it is difficult to know the true costs associated with DBD or type 3 DCD liver transplant, which include not only organ recovery but also time spent in the ICU between the potential donor's identification and the donation itself. Although it is impossible to know for certain, there is a chance that the costs associated with procuring organs from type 2 DCD donors are actually less that those associated with DBD or type 3 DCD donors, given that the care of a patient in the former context is limited to a few hours versus several days of highly costly care in the latter.

Causes for rejecting type 2 DCD livers were classified according to a system to differentiate absolute from relative contraindications. Donor contraindications included problems inherent to the donor that would always contraindicate the use of the liver and were absolute. Familial or judicial refusal of consent also indicated absolute contraindication. Technical or logistical failures had to do with an inability to perform a step of the protocol, namely NECMO. Based on experimental work (17–20) and inferior clinical results without advanced organ maintenance (8), we consider NECMO critical for obtaining viable livers from type 2 DCD donors (14). The impossibility of performing NECMO due to impaired venous return, vascular trauma or pump failure was an absolute contraindication.

Suboptimal evolution encompassed contraindications that were based on our best estimates as to which evolutionary factors indicated hepatic viability. Although they were based in experimental and clinical work, they were all relative. We established limits on the lengths of each phase of the protocol and the levels of hepatic transaminases during NECMO and turned down livers that were poorly perfused to avoid grafts that had suffered significant warm ischemia, considering they would be subjected to additional cold ischemia. Furthermore, we considered steatotic grafts to be too high-risk, based on a theory of multiple hits.

Overall, the single most important reason for rejecting one of these livers was inadequate venous return during NECMO. Inadequate venous return likely occurred secondary to unrecognized vascular trauma or internal hemorrhage. In addition, collapse of the inferior vena cava could have impeded flow into the reservoir. For this reason, we insist on seeing the catheter tip just below the diaphragm on the chest radiograph to ensure it is located at the outflow orifices of the hepatic veins. In this position, it is optimally situated to collect splanchnic blood return; the diaphragm also provides some support here, making caval collapse less likely. Finally, although the incidence of

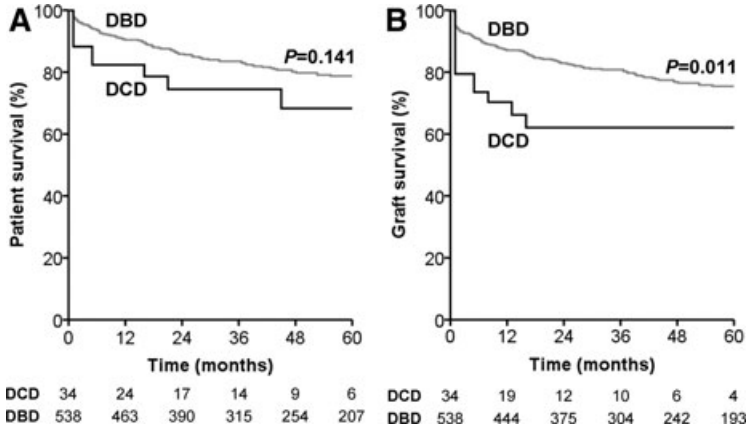


Figure 4: Kaplan–Meier curves for (A) patient and (B) graft survival for type 2 DCD and primary DBD liver transplants performed between April 2002 and December 2010 (N = 34 and 538, respectively). The tables below the curves reflect the number of patients at risk in each group at each postoperative time point.

inadequate venous return likely would have been less if we had run the pump at a lower flow rate, we insist on at least 1.7 L/min, based on experimental studies demonstrating worse outcomes with lower flows (21).

As a category, suboptimal evolution was the most important contraindication and the reason for which 32% of livers were not used. This is interesting, given that it was the only category comprised of relative contraindications and, therefore, represents a potential area for improvement. The standards we use to evaluate the evolution of a potential DCD liver are not fixed; by expanding them, we may be able to use more livers, though doing so could also lead to more graft failures and lower survival. Employing advanced means of liver preservation, such as *ex vivo* normothermic machine perfusion (NMP), is another option to increase the applicability of type 2 DCD liver transplant (22,23). In a porcine model of DCD liver transplant, we demonstrated that the sequential use of NECMO and NMP significantly improved hepatic injury, inflammation and function versus NECMO followed by cold storage (24). By providing continuous physiological metabolism, NMP not only allows us to evaluate and maintain damaged grafts, but it also offers the opportunity to treat and improve them before transplantation (19,25).

Another step that could improve the applicability of type 2 DCD liver transplantation is the use of thrombolytics. During cardiac arrest, red-cell stasis in the hepatic microvasculature leads to the formation of microthrombi, which cause ongoing ischemia even when gross blood flow is restored. Administering an anticoagulant, such as heparin, helps prevent propagation of these clots, whereas administering a thrombolytic should cause them to lyse (26,27). Currently, we administer heparin after the declaration of death but do not give thrombolytics. If we were to employ thrombolytics during NECMO, however, we could potentially restore hepatic microvascular flow and, consequently, graft viability. Studies are needed to confirm this.

Among type 2 DCD livers that were ultimately transplanted, 1-year patient and graft survivals were 82% and 70%, respectively. Though graft survival was inferior to that associated with primary DBD liver transplant, these results are comparable to those achieved with type 3 DCD livers (28). For type 3 DCD livers, 1-year patient and graft survivals are 74–92% and 54–80%, respectively (29–39). Graft survival also improved from the first half of our series to the second. Apart from increased experience with the protocol, this may be due to the fact that recipients in the first half were sicker at the time of transplant than those in the second. Also, the technology used for donor maintenance improved with time. In 2008, manual chest compressions were replaced with mechanical ones. Mechanical compressions have been associated with less "hands-off" time and higher perfusion pressures during CPR (40–42).

Liver transplant recipients that develop IC present within the first few months with jaundice, pruritis and/or cholangitis; when treated conservatively, they may become severely malnourished. Furthermore, they are hospitalized more often and subjected to more invasive procedures versus recipients without IC (43). We had a low threshold to relist these patients, to give them the best chance for a successful retransplantation outcome. Three patients (8%) developed IC and were retransplanted at a median of 8 months. These results are comparable to those reported for type 3 DCD liver transplantation. Among the most important series published to date, rates of IC developing in type 3 DCD livers have ranged from 11% to 50% (29–35,37–39).

Type 2 DCD donors, if properly maintained, can offer similar outcomes to type 3. Type 2 donors also offer several advantages. If cardiac arrest is witnessed and emergency medical services rapidly mobilized, the period of warm ischemia may actually be shorter in type 2 versus type 3 DCD, because donors in the latter group typically suffer extended prearrest hypotension that is beyond the control of the transplant team (44–46). In addition, type 2 donors generally come from outside the hospital, not the ICU, and are healthier at the time of donation. Another advantage of type 2 DCD is that it does not detract from the pool of potential DBD donors. A type 2 donor can never be converted to a DBD donor, whereas, in some cases, a type 3 donor could become a DBD donor if brain death is waited for, an important fact that has significant implications regarding the number of organs recovered (on average, more for DBD than DCD; Ref. 47). Finally, ethical concerns surrounding type 2 DCD are fewer, as the donor has died naturally and not secondary to the active removal of life support (48,49). However, one aspect of our protocol that may raise ethical concerns has to do with heparinizing and cannulating the potential donor.

According to Spanish law, after the declaration of cardiorespiratory death, measures should be taken to ensure the organ viability before initiating the consent process (14). Hence, although consent is obtained for the ultimate donation, techniques such as heparinization and cannulation should be performed before contacting the family. Although US laws are distinct, it seems that there are legal means by which potential type 2 DCD donors could be heparinized and cannulated there, as well. According to the Uniform Anatomical Gift Act (UAGA; Ref. 50), wallet-sized donor cards, often part of states' driver's licenses, are legal documents that permit the postmortem recovery of organs. Furthermore, the UAGA affirms the priority of the deceased's wishes over those of the family, and donor cards take legal precedence over a family's refusal to donate. In the setting of type 2 DCD, in which potential donors almost always arrive to the hospital unaccompanied, donor cards could provide consent to perform the steps necessary to maintain organ viability in lieu of direct contact with the potential donor's next-of-kin.

In summary, transplantation using type 2 DCD livers is a viable alternative to standard criteria liver transplant. Despite its estimated potential, the clinical applicability of type 2 DCD liver transplant is only around 9%. However, by expanding the criteria we use to evaluate these livers or by employing NMP or thrombolytics, we may be able to significantly increase the yield of transplantable livers from this source.

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Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

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