



University of Modena Experience With Liver Grafts From Donation After Circulatory Death: What Really Matters in Organ Selection?

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ABSTRACT

Introduction. The use of grafts from donation after circulatory death (DCD) is an important additional source to implement within the donor pool. We herein report the outcomes of our early experience with DCD grafts for liver transplantation (LT).

Methods. Ten patients successfully underwent LT with grafts from DCD donors between August 2017 and January 2019 at the Hepato-Pancreato-Biliary Surgery and Liver Transplant Unit of University of Modena and Reggio Emilia. All donors underwent normothermic regional perfusion after death declaration and, after the procurement, all the suitable grafts underwent ex situ hypothermic perfusion prior to transplantation.

Results. Mean postoperative hospital stay after transplant was 12.7 days (range, 5-26), and in 5 cases we placed a biliary drainage (Kehr tube) during surgery. Primary graft nonfunction did not occur after LT in this cohort, although, we registered one case of biliary anastomosis stricture that was managed endoscopically by endoscopic retrograde cholangiopancreatography. All patients are alive and none required retransplantation.

Conclusions. In our experience with controlled DCD donors, the demonstration of: (1) a negative trend of lactate during normothermic regional perfusion; (2) an aspartate aminotransferase and alanine aminotransferase level lower than 2000 mU/dL; and (3) less than 1 hour of functional warm ischemia time along with no signs of microscopic or macroscopic ischemia of the grafts, are related to positive outcomes in the first year after transplant. A DCD risk score based on Italian population characteristics and regulations on death observation may improve donor-recipient match and avoid futile transplants.

IN the setting of organ donor shortage, the use of grafts coming from donation after circulatory death (DCD) has been presented as an important additional source to implement within the donor pool [1]. Moreover, it does not represent an absolute novelty, since this practice was the only available option until the Harvard definition of brain death was established, as reported by Starzl et al [2]. Currently, the use of these organs has grown in acceptance in many different countries [3], however, results of liver transplantation (LT) from these donors are not uniform

among the different experiences. Notably, this could be the consequence of a patchy series including uncontrolled DCDs (Maastricht categories I and II) [4], that are related

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to a higher degree of complexity, leading to a difficult evaluation of the graft with a potential negative effect on the series' outcome.

It has been claimed that the Italian regulations on cardiac death declaration (20 consecutive minutes of no-touch interval to demonstrate cardiac flatline at the electrocardiogram) may negatively impact the use of DCD donors in our country [5]. We herein report our experience analyzing the outcomes of DCD grafts for LT.

METHODS

The program for the implementation of the use of DCD grafts started in our institution, the University of Modena and Reggio Emilia, in 2017. Ten patients successfully underwent LT with grafts from DCD donors between August 2017 and January 2019 at the Hepato-Pancreato-Biliary Surgery and Liver Transplant Unit of University of Modena and Reggio Emilia. In detail, 9 were donations from controlled DCD (cDCD), and 1 from uncontrolled DCD (uDCD). Moreover, of the 8 cDCD, 6 donations happened inside our institution, at the intensive care unit of Baggiovara Hospital, the University Hospital of Modena, Italy.

In all DCDs, we closely monitored functional warm ischemia time (fWIT), that starts when oxygen saturation falls below 70% or systolic blood pressure falls below 50 mm Hg, and finishes as the normothermic regional perfusion (NRP) is activated.

All donors underwent NRP after death declaration, with average duration of 252.6 minutes (range [min], 150-624) with an ideal flow of 2 L/min at least. Blood exams were carried out during perfusion at predetermined checkpoints to evaluate alanine aminotransferase (ALT), aspartate aminotransferase (AST), and lactate. In detail, arterial blood gas tests are carried out every 30 minutes and complete blood tests hourly.

During the study period we discarded 6 DCD grafts: (1) 4 cDCDs were declined at the procurement operation because of their macroscopic appearance (diffuse ischemia) or negative histologic features at liver biopsies (Ishak \geq 3, macrovesicular steatosis \geq 30%, arteriolar status, diffuse presence of necrosis); (2) 1 cDCD was declined because it was procured and perfused with a hypothermic oxygenated machine 12 hours before being offered to our center; and (3) 1 uDCD was declined due to the unknown past medical history.

After the procurement, all the suitable grafts underwent ex situ hypothermic perfusion using Liver Assist (Organ Assist, Groningen,

Netherlands) before transplantation with machine perfusion (MP) through both arterial and portal circulation at an average temperature of 10°C. Indication to place a Kehr tube was determined at the time of transplant based on the bile production after revascularization of the liver graft.

RESULTS

Donors Features

Donors characteristics are summarized in Table 1. Donors mean age was 55.8 years (range, 35-67), 7 men and 3 women, and mean functional ischemia time was 38.1 minutes. Evaluation of blood aminotransferases and lactate during NRP revealed maximum values of 1630/1332 U/L for AST/ALT and 20 mmol/L for lactate. Liver biopsies were performed in all cases to assess the steatosis and the arteriolar status of the graft. During the procurement operation, all grafts were perfused with 7 L of Celsior solution (IGL, Lissieu, France) through the arterial cannula of NRP.

Recipients Features

Recipients characteristics are summarized in Table 2. Patients mean age was 55.8 (range, 48-60), male to female ratio 9:1, and Model for End-Stage Liver Disease score at transplant time ranged from 6 to 14. Eight patients received the transplant due to hepatocellular carcinoma, and 1 case eventually resulted to be a combined hepatocellular cholangiocarcinoma at the final histology, while 2 patients had hepatitis C virus-related liver cirrhosis with human immunodeficiency virus coinfection. The average duration of hypothermic perfusion of the graft was 127.4 minutes (range, 88-212), and the average pressure of perfusion was 28 mm Hg through the artery and 5.5 mm Hg through the venous cannula. Mean postoperative hospital stay after transplant was 12.7 days (range, 5-26), and in 5 cases we placed a biliary drainage (Kehr tube) during surgery. No primary graft nonfunction (PNF) after LT occurred in this cohort, while we registered 1 case of biliary anastomosis stricture that was managed endoscopically by endoscopic retrograde cholangiopancreatography. One patient developed a biliary stricture after Kehr tube removal requiring a re-operation to perform a Roux en-Y

Table 1. Donor Features

Sex	Age (y)	Controlled/Uncontrolled	BMI (kg/m ²)	fWIT (min)	NRP (h, min)	CIT (h, min)	Duration Ex Situ Perfusion (h, min)	Lactate Trend T0-T2 (mmol/L)	AST/ALT Peak (IU/L)*
M	35	Uncontrolled	23	NA	10, 24	7, 50	3, 18	16-20	238/- (T0)
M	57	Controlled	25	50	4, 15	6, 20	1, 28	12.8-7.6	61/35 (T4)
F	65	Controlled	23	34	3, 20	7, 25	1, 30	7.12-7.27	-/37 (T2)
F	44	Controlled	25	36	2, 30	8, 20	2, NA	12.6-10.7	68/34 (T0)
M	63	Controlled	24	50	4, 40	5, 56	1, 30	12.4-12.2	1630/1332 (T3)
M	58	Controlled	22	40	2, 38	6, 45	1, 55	12.4-10.4	122/107 (T2)
M	60	Controlled	23	33	2, 30	7, NA	2, 57	14.2-8.8	73/89 (T3)
M	66	Controlled	28	30	4, 50	9, 32	1, 33	10.4-5	39/21 (T1)
F	67	Controlled	25	36	3, 26	7, 30	3, 32	11-8	31/22 (T1)
M	57	Controlled	26	34	3, 33	7, 30	1, 31	9.9-4.3	112/- (T2)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CIT, cold ischemia time; F, female; fWIT, functional warm ischemia time; M, male; NA, not applicable; NRP, normothermic regional perfusion.

*In the last column, the left value is refers to AST, the right value is ALT, and T is the time when transaminase peak was registered during NRMO after ECMO started.

Table 2. Recipient Features

Sex	Age (y)	Indication to LT	MELD at LT	Portal Vein Thrombosis	Kehr Tube	Hospital Stay (d)	Complications/Treatment
M	56	HCC/HCV	10	Yes (grade II)	Yes	16	Biliary stricture after Kehr removal/Hepaticojejunostomy
M	55	HCC/HCV	9	No	Yes	9	NA
M	58	HCC/ASH	14	Yes (grade I)	Yes	26	Biliary leak after Kehr removal/ERCP
M	55	HCC/HCV	8	No	Transcystic tube	13	NA
M	60	HCC/HCV	9	No	Yes	9	Biliary leak after Kehr removal >> ERCP
M	48	cHCC-CC	7	No	No	5	Biliary stricture >> ERCP
M	59	HCV-HIV coinfection-intrahepatic biliary lithiasis	6	No	No	9	Wound infection
M	52	HCC/HCV	7	No	No	9	NA
F	56	HCV/HIV	7	Yes (grade I)	No	19	Ascites
M	59	HCC/HCV	9	No	No	12	NA

Abbreviations: ASH, alcoholic steatohepatitis; cHCC-CC, combined hepatocellular cholangiocarcinoma; ERCP, endoscopic retrograde cholangiopancreatography; F, female; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LT, liver transplantation; M, male; MELD, Model for End-Stage Liver Disease; NA, not applicable.

hepaticojejunostomy, while 2 patients showed bile leak after Kehr removal and were treated by endoscopic placement of biliary stent. All patients are alive and none required retransplantation.

DISCUSSION

Many single-center studies have highlighted comparable outcomes between DCD and donation after brain death (DBD) [6,7,8,9]. The major concerns related to the use of DCD grafts for LT are related to the increased risk of developing ischemic cholangiopathy (IC), PNF, and delayed graft function (DGF) [10,11]. The mechanism of injury has been found in prolonged warm ischemia time, which determines an enhanced ischemia-reperfusion damage [4]. MP of the liver grafts prior to transplantation has shown encouraging results in reducing morbidity after LT using DCD grafts. It has been demonstrated that hypothermic oxygenated perfusion is superior to static cold storage in preventing alteration of graft function and the development of IC [12]. Moreover, MP allows further evaluations of the graft during perfusion in order to assess its transplantability.

New strategies including normothermic MP or sequential hypothermic and normothermic MP have been described showing reduction of IC and DGF, improving the outcomes of marginal grafts and DCD organs [13,14]. The challenge posed by our national regulation on cardiac death declaration is the potential prolonged warm ischemia time that may negatively impact on LT outcome, together with fWIT that occurs in the agonal phase after suspension of resuscitation measures. Therefore, we need to develop adequate strategies to minimize fWIT and warm ischemia time, preserving liver function. This study is unique in the setting of the experiences reported to date in the literature because it shows that it is possible to achieve good perioperative outcomes even in the context of a 20-minute no-touch interval. Moreover, it is the result of a synergic work of both regional and local authorities together with health care professionals, with the aim to expand the donor pool and the chance for

patients on the waiting list to receive a transplant. In our experience with cDCD donors, the demonstration of: (1) a negative trend of lactate during NRP; (2) AST and ALT lower than 2000 mU/dL; and (3) less than 1 hour of fWIT are related to positive outcomes in the first year after transplant. However, a crucial step is the macroscopic evaluation of the graft during the procurement operation, which should be of regular shape, consistency, and color, without signs of ischemia of the parenchyma. As a matter of fact, a large survey among LT centers in the United States showed that up to 71% of the centers do not accept DCD livers procured by other teams, while an additional 14% of the centers only accepts livers procured by donor surgeons whom they know [15]. A well-designed protocol and a close collaboration between all the professionals involved (anesthesiologists, transplant surgeons, and perfusionists) is crucial for the good outcome of the donation. Adequate donor-recipient matching must be carefully taken into account as reported by Muiesan et al [16]: this could be the key factor to restrain bad outcomes when dealing with DCD donations.

However, there are some limitations to the application of the UK DCD risk score in Italy, mainly related to the no-touch interval of 20 minutes, therefore, we would benefit from the creation of a scoring system to predict transplant futility based on our national regulations and donors average characteristics. Notably, donors and recipients in our cohort would have fallen in the high risk or futility category of the UK score just because of the fWIT, while the outcomes proved to be more than satisfactory.

CONCLUSIONS

Currently, we are far from defining an optimal indication to the use of DCD donors, however, patients in good general condition with low Model for End-Stage Liver Disease and hepatocellular carcinoma at risk of drop out may benefit from this allocation.

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REFERENCES

- [1] Monbaliu D, Pirenne J, Talbot D. Liver transplantation using donation after cardiac death donors. *J Hepatol.* 2012;56:474–485.
- [2] Starzl TE, Marchioro TL, Porter KA, Brettschneider L. Homotransplantation of the liver. *Transplantation.* 1967;5:790–803.
- [3] Rady MY, Verheijde JL, McGregor J. Organ donation after circulatory death: the forgotten donor? *Crit Care Lond Engl.* 2006;10:166.
- [4] Cursio R, Gugenheim J. Ischemia-reperfusion injury and ischemic-type biliary lesions following liver transplantation. *J Transplant.* 2012;2012:164329.
- [5] Geraci PM, Sepe V. Non-heart-beating organ donation in Italy. *Minerva Anesthesiol.* 2011;77:613–623.
- [6] Vanatta JM, Dean AG, Hathaway DK, Nair S, Modanlou KA, Campos L, et al. Liver transplant using donors after cardiac death: a single-center approach providing outcomes comparable to donation after brain death. *Exp Clin Transplant.* 2013;11:154–163.
- [7] Grewal HP, Willingham DL, Nguyen J, Hewitt WR, Taner BC, Cornell D, et al. Liver transplantation using controlled donation after cardiac death donors: an analysis of a large single-center experience. *Liver Transplant.* 2009;15:1028–1035.
- [8] Fujita S, Mizuno S, Fujikawa T, Reed AI, Kim RD, Howard RJ, et al. Liver transplantation from donation after cardiac death: a single center experience. *Transplantation.* 2007;84:46–49.
- [9] De Carlis R, Di Sandro S, Lauterio A, Ferla F, Dell'Acqua A, Zanierato M, et al. Successful donation after cardiac death liver transplants with prolonged warm ischemia time using normothermic regional perfusion. *Liver Transplant.* 2017;23:166–173.
- [10] Mourad MM, Algarni A, Liossis C, Bramhall SR. Aetiology and risk factors of ischaemic cholangiopathy after liver transplantation. *World J Gastroenterol.* 2014;20:6159–6169.
- [11] De Carlis R, Di Sandro S, Lauterio A, Botta F, Ferla F, Andorno E, et al. Liver grafts from donors after circulatory death on regional perfusion with extended warm ischemia compared with donors after brain death. *Liver Transplant.* 2018;24:1523–1535.
- [12] Dutkowski P, Polak WG, Muiesan P, Schlegel A, Verhoeven CJ, Scalera I, et al. First comparison of hypothermic oxygenated perfusion versus static cold storage of human donation after cardiac death liver transplants: an international-matched case analysis. *Ann Surg.* 2015;262:764–770.
- [13] de Vries Y, Matton APM, Nijsten MWN, Werner MJM, van den Berg AP, de Boer MT, et al. Pretransplant sequential hypo- and normothermic machine perfusion of suboptimal livers donated after circulatory death using a hemoglobin-based oxygen carrier perfusion solution. *Am J Transplant.* 2019;19:1202–1211.
- [14] Nasralla D, Coussios CC, Mergental H, Akhtar MZ, Butler AJ, Ceresa CDL, et al. A randomized trial of normothermic preservation in liver transplantation. *Nature.* 2018;557:50–56.
- [15] Sher L, Quintini C, Fayek SA, Abt P, Lo M, Yuk P, et al. Attitudes and barriers to the use of donation after cardiac death livers: comparison of a United States transplant center survey to the united network for organ sharing data. *Liver Transpl.* 2017;23:1372–1383.
- [16] Schlegel A, Kalisvaart M, Scalera I, Laing RW, Mergental H, Mirza DF, et al. The UK DCD Risk Score: a new proposal to define suitability in donation-after-circulatory-death liver transplantation. *J Hepatol.* 2018;68:456–464.