# Hypothermic Oxygenated Perfusion Versus Normothermic Regional Perfusion in Liver Transplantation From Controlled Donation After Circulatory Death

## *First International Comparative Study*

*Xavier Muller, MD,*† Kayvan Mohkam, MD, PhD,* Matteo Mueller, MD,† Andrea Schlegel, MD,† Federica Dondero, MD,‡ Ailton Sepulveda, MD,‡ Eric Savier, MD,§ Olivier Scatton, MD, PhD,§ Petru Bucur, MD, PhD,¶ Ephrem Salame, MD, PhD,¶ Heithem Jeddou, MD,|| Laurent Sulpice, MD, PhD,|| Gabriella Pittau, MD,** Marc-Antoine Allard, MD, PhD,** Jean-Yves Mabrut, MD, PhD,* Philipp Dutkowski, MD,† Pierre-Alain Clavien, MD, PhD,† and Mickael Lesurtel, MD, PhD*✉*

**Objective:** To compare HOPE and NRP in liver transplantation from cDCD.

**Summary of Background Data:** Liver transplantation after cDCD is associated with higher rates of graft loss. Dynamic preservation strategies such as NRP and HOPE may offer safer use of cDCD grafts.

**Methods:** Retrospective comparative cohort study assessing outcomes after cDCD liver transplantation in 1 Swiss (HOPE) and 6 French (NRP) centers. The primary endpoint was 1-year tumor-death censored graft and patient survival.

**Results:** A total of 132 and 93 liver grafts were transplanted after NRP and HOPE, respectively. NRP grafts were procured from younger donors (50 vs 61 years, $P < 0.001$), with shorter functional donor warm ischemia (22 vs 31 minutes, $P < 0.001$) and a lower overall predicted risk for graft loss (UK-DCD-risk score 6 vs 9 points, $P < 0.001$). One-year tumor-death censored graft and patient survival was 93% versus 86% ($P = 0.125$) and 95% versus 93% ($P = 0.482$) after NRP and HOPE, respectively. No differences in non-anastomotic biliary strictures, primary nonfunction and hepatic artery thrombosis were observed in the total cohort and in 32 vs. 32 propensity score-matched recipients

**Conclusion:** NRP and HOPE in cDCD achieved similar post-transplant recipient and graft survival rates exceeding 85% and comparable to the benchmark values observed in standard DBD liver transplantation. Grafts in the HOPE cohort were procured from older donors and had longer warm ischemia times, and consequently achieved higher utilization rates. Therefore, randomized controlled trials with intention-to-treat analysis are needed to further compare both preservation strategies, especially for high-risk donor-recipient combinations.

**Keywords:** DCD, graft preservation, liver transplantation, machine perfusion, organ donation

(*Ann Surg* 2020;272:751–758)

Liver transplantation (LT) from controlled donation after cardiac death (cDCD) is a promising strategy to rescue patients with end-stage liver disease and reduce waiting-list dropout.[1] During the cDCD process, however, periods of hypoperfusion and circulatory arrest in the donor expose the liver graft to deleterious warm ischemic injury which may impair its functionality after transplantation.[2–3] Consequently, recipients of cDCD grafts present an increased risk of graft loss mainly related to higher rates of primary non function or biliary complications, notably non-anastomotic strictures, with the need of re-transplantation.[4–6]

To reduce the risk associated with cDCD grafts while respecting local ethical and regulatory constraints of the donation process around the world, 2 main dynamic preservation strategies have been implemented in clinical practice, that is, normothermic regional perfusion (NRP) and hypothermic oxygenated perfusion (HOPE).[7]

NRP in the donor before liver graft procurement followed by static cold storage may reduce the incidence of both graft loss and ischemic-type biliary complications after cDCD LT.[8–9] It can additionally be beneficial for several types of organs from the same donor. Another preservation strategy is to apply static cold storage followed by end-ischemic HOPE of liver grafts after procurement.[10] HOPE has been shown to allow transplantation of very high-risk cDCD donor-recipient combinations.[11] Despite these promising results a direct comparison is lacking. Thus, this study aims at providing the first international multicentric large-scale comparison of outcomes after NRP and HOPE in cDCD LT.

## METHODS

### Study Design

This is a retrospective study comparing outcomes after cDCD LT in one NRP cohort from 6 high-volume French centers and one HOPE cohort from the University Hospital of Zurich, Switzerland.

From the *Department of Surgery and Liver Transplantation, Croix-Rousse University Hospital, University of Lyon I, Lyon, France; †Department of Surgery, Swiss Hepatopancreatobiliary and Transplantation Center, University Hospital Zurich, Zurich, Switzerland; ‡Department of Hepatobiliopancreatic Surgery, APHP, Beaujon Hospital, Clichy, France; §Department of Hepato-biliary Surgery and Liver Transplantation, Sorbonne Université Pitié-Salpêtrière Hospital, Paris, France; ¶Department of Digestive, Oncological, Endocrine, Hepato-Biliary, Pancreatic and Liver Transplant Surgery, Trousseau Hospital, Tours, France; ||Department of Hepatobiliary and Digestive Surgery, Pontchaillou University Hospital, Rennes, France; and **Centre Hépato-Biliaire, AP-HP, Hôpital Paul Brousse, Université Paris Sud, Villejuif, France.

✉mickael.lesurtel@chu-lyon.fr.

X.M. and K.M. contributed equally as first authors.

M.L., P.A.C., and P.D. contributed equally as senior authors.

X.M., K.M., P.D., and M.L. designed the study, acquired the data, performed the statistical analysis, interpreted the data, and wrote the manuscript. P.A.C. and J.Y.M. interpreted the data, critically reviewed the data and drafted a final version of the manuscript. M.M. acquired, analyzed, interpreted and verified the center data and critically reviewed the manuscript. A.S., F.D., A.S., E.S., O.S., P.B., E.S., H.J., L.S., G.P., M.A. acquired, analyzed, interpreted, and verified the individual center data and approved the final manuscript.

The authors declare no conflict of interest.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.annalsofsurgery.com).



ISSN: 0003-4932/20/27205-0751

DOI: 10.1097/SLA.0000000000004268

The study period covered 4 years (2015–2019) for the French cohort and 6 years (2012–2019) for the Zurich cohort. Outcomes were assessed until January 1, 2020.

The cDCD program in France is a national program and procurement of liver grafts in the setting of cDCD is exclusively performed with NRP. All French centers included in this study follow the same cDCD procedure standardized by the national organ donation agency.[12] The French authorities chose a step-up approach in the selection of cDCD donors, for example limiting donor age to <61 years until May 2017 followed by <66 years until June 2018 and currently <71 years. Detailed criteria were: planned cold ischemia time (CIT) ≤8 hours, donor age ≤71 years, functional donor warm ischemia (fDWI) time <45 minutes and no-flow <25 minutes, liver transaminases (AST or ALT) increase less than 4 times the upper normal value during NRP, liver graft biopsy with frozen section showing macrovesicular steatosis <20%, and at least 60 minutes of NRP.[13]

The cDCD program in Switzerland has been established in 2012. In contrast to the French program selection of grafts was exclusively performed during HOPE, based on data from animal models and recent advances in assessment of mitochondrial metabolism (Supplementary material, http://links.lww.com/SLA/C422).[14–16]

## In-situ NRP

NRP is an extra-corporeal membrane oxygenation based perfusion system applied to the donor before the start of organ procurement. After cardiac arrest of the donor, a ''no-touch'' period of 5 minutes was mandatory before brain death could be declared. Femoral artery cannulas were then introduced over pre-placed guidewires to reconstitute blood flow at physiological temperatures to the potential donor organs (postmortem vessel cannulation). Of note, on treatment withdrawal heparin (300 UI/kg) was administered to the donor to prevent blood clotting. The minimal required duration of NRP for the procurement to proceed was 60 minutes. Once NRP was terminated, organs were cold flushed and a standard procurement followed by static cold storage was performed (Supplementary material, http://links.lww.com/SLA/C422).

## Ex-vivo HOPE

In the setting of HOPE, super rapid en bloc multiorgan retrieval was performed. After documentation of circulatory arrest, brain death diagnosis was confirmed after a no-touch period of 10 minutes (lowered to 5 minutes since 2018). Importantly, no heparin was administered to the donor at treatment withdrawal. After brain death diagnosis, the iliac artery was cannulated unilaterally after laparotomy and the organs were cold flushed with Institute-George-Lopez-1 solution. Static cold storage was used to transport the graft to the transplant center.

After back-table preparation, HOPE was performed using the Liver Assist device (Organ Assist). Ex-vivo liver perfusion was performed through the portal vein only, with active oxygenation and low pressure and flow (3 mm Hg, 150–300 mL/min). The University of Wisconsin Machine Perfusion solution (Belzer MPS) was used as perfusion solution for all HOPE procedures (Supplementary material, http://links.lww.com/SLA/C422). After 30 minutes of perfusion, liver graft quality was assessed by fluorescence spectroscopic analyses of the perfusate, as previously described.[16]

## Endpoints and Definitions

The primary endpoint was 1-year tumor-death censored graft and patient survival.

Secondary endpoints included early graft function indicators (International normalized ratio, factor V), level of liver transaminases (ALT, AST) and the composite score for early allograft dysfunction (EAD) by Olthoff et al.[17]

Functional donor warm ischemia (fDWI) time was defined as duration from mean arterial blood pressure below 50 mm Hg to cold aortic perfusion in the HOPE cohort and mean arterial blood pressure below 45 mm Hg to initiation of the perfusion in the NRP cohort. Asystolic warm ischemia started at the occurrence of cardiac arrest.

We defined 3 main phases of liver graft preservation: (1) duration of static cold storage which is common to HOPE and NRP, (2) duration of HOPE or NRP, and (3) total ex-vivo preservation which is defined as the time from aortic cross-clamp in the donor to graft reperfusion in the recipient.

Liver graft utilization rate was defined as the proportion of liver grafts which were transplanted after initiation of therapeutic withdrawal in donors eligible for liver graft donation.

Non-anastomotic biliary stricture (NAS) was defined as either multifocal, unifocal intrahepatic, or hilar strictures with or without the presence of concomitant hepatic artery thrombosis (HAT) or arterial complications. NAS was detected clinically and confirmed by magnetic resonance cholangiography.

## Statistical Analysis

Categorical variables are expressed in quantities and percentages and continuous variables are expressed as median with interquartile range. Continuous variables were compared using the Mann-Whitney *U* test. Categorical variables were compared using the Chi-square test or the Fisher exact test. *P*-values $< 0.05$ were considered statistically significant. Survival rates were estimated using Kaplan-Meier methods, with comparisons between groups performed using log-rank tests.

To adjust for covariate imbalances between the 2 groups, we performed a propensity score matching. The propensity score was calculated using a non-parsimonious binary logistic regression model, with treatment allocation as endpoint (NRP vs HOPE) and the 6 UK DCD Score variables (donor age, donor body mass index, recipient age, fDWI time, and CIT) as covariates.[5] (Details in Supplementary Material, http://links.lww.com/SLA/C422). Approval by the French institutional local and national ethics committee and approval by the local Swiss ethics committee were obtained (KEK 2019-0100).

# RESULTS

During the study period, 132 and 93 cDCD liver grafts were successfully procured and transplanted after NRP and HOPE, respectively. Due to more stringent donor selection criteria in the NRP cohort, the liver graft utilization rate was significantly lower compared to the HOPE cohort (63% vs 81%, $P < 0{,}001$, Fig. 1). Median post-LT follow-up was 20 [interquartile range (IQR) 9–25] and 28 (IQR 15–248) months for NRP and HOPE, respectively.

HOPE livers were procured from older donors (61 vs 50 years, $P < 0.0001$) with longer fDWI times (31 vs 22 minutes, $P < 0.001$) resulting in a higher donor risk index (DRI) (2.47 vs 2.01, $P < 0.001$) (Table 1). In the NRP cohort, procurement started after median 184 minutes of NRP in the donor, followed by static cold storage for 5.7 (IQR 4.7–6.6) hours before implantation. HOPE liver grafts first underwent 4 (IQR 3.1–5) hours of cold storage followed by a median 132 minutes HOPE perfusion and subsequent transplantation. Median total ex-vivo preservation was 5.7 and 6.4 hours after NRP and HOPE, respectively ($P < 0.001$).

Overall, recipients had low labMELD scores with 55% and 45% presenting hepatocellular carcinoma in the NRP and HOPE group, respectively ($P = 0.96$). Overall, donor-recipient combination presented a higher predicted risk of graft loss in the HOPE cohort (UK-DCD-risk score 6 vs 9 points, $P < 0.001$) (Table 2).

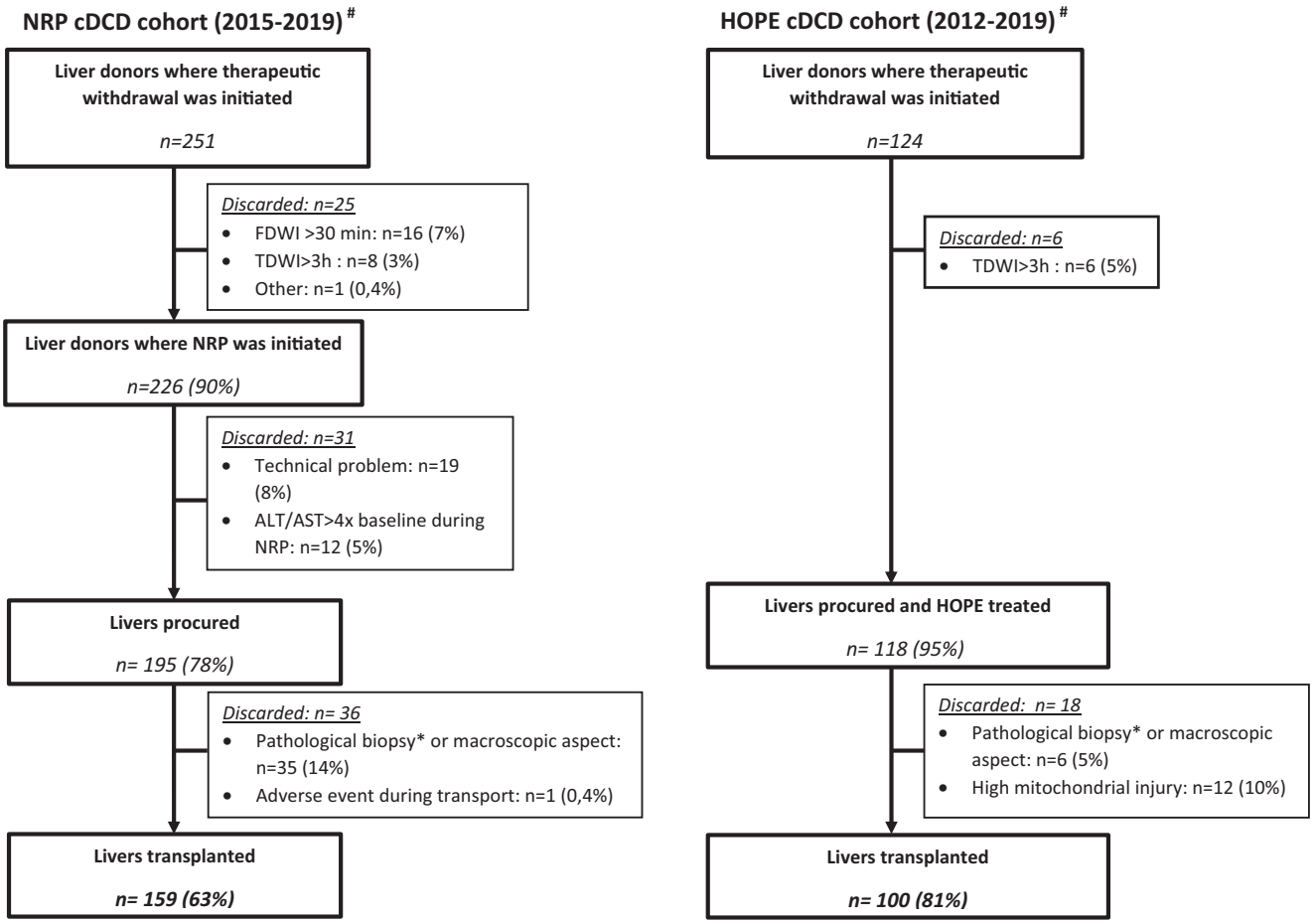



**FIGURE 1.** Liver graft utilization rates and reasons for graft discard. #To give a complete overview we included all the donors and liver grafts until January 1, 2020 in this figure. The total number is consequently greater than the actual study population for which the follow-up ended on the 01.01.2020. *In NRP pathological biopsy was defined as cirrhosis, fibrosis >F1, macrosteatosis >20%. In HOPE pathological biopsy was defined as cirrhosis, fibrosis >F1, macrosteatosis >60%. FDWI indicates functional donor warm ischemia; HOPE, hypothermic oxygenated perfusion; NRP, normothermic regional perfusion; TDWI, total donor warm ischemia.

## Early Graft Function and Injury

Serum ALT and AST release peaked during the first 24 hours after transplantation with higher median peak values after HOPE (ALT 1197 vs 594; AST 1302 vs 489, $P < 0.001$; Supplementary Material Fig. S1, http://links.lww.com/SLA/C422). This translated into 68% of EAD in the HOPE cohort compared to 20% in the NRP cohort ($P < 0.001$). Synthetic liver function expressed by factor V and INR improved rapidly over the first 48 hours post-LT for both cohorts reaching a plateau after postoperative day 5. ALT/AST levels decreased to similar levels in both groups (Fig. 2).

## Graft and Patient Survival

One-year tumor-death censored graft and patient survival was 93% versus 86% and 95% versus 93% after NRP and HOPE, respectively ($P = 0.12$; $P = 0.48$) (Fig. 3). No significant differences were observed for NAS (4.5% vs 8.6%, $P = 0.22$), primary non function (2.3% vs 4.3% $P = 0.39$) and HAT (3% vs 2.2%, $P = 0.69$) between NRP and HOPE, respectively (Table 3).

## Risk Adjusted Donor-recipient Combinations

After propensity-score matching of donor and recipient risk factors for graft loss, a subgroup analysis was performed with 32 cases in each group. After matching, both cohorts presented with comparable fDWI time (27 minutes), donor age (58 vs 59 years) and cold ischemia time (HOPE 285 minutes vs NRP 309 minutes) resulting in a median UK-DCD risk score of 8 in both cohorts (IQR HOPE 6–11; IQR NRP 5–9) (Supplementary Material Fig. S2, http://links.lww.com/SLA/C422). Transaminase release remained higher in the HOPE cohort but 1-year tumor-death censored graft survival was still comparable (93% vs 87.3% for NRP and HOPE, $P = 1$). Importantly, rates of NAS, HAT, and primary non-function (PNF) remained similar in both cohorts. Serum creatinine levels at post-LT day 7 were higher after HOPE (111 vs 68 μmol/L, $P = 0.01$) but renal replacement rates were not significantly different (Table 3).

## DISCUSSION

This is the first large-scale international multicentric study comparing 2 different preservation strategies, NRP and HOPE, in cDCD LT. Both, NRP and HOPE disclosed 1-year tumor-death censored graft survival rates >85% with similar rates of NAS, HAT, and PNF, comparable to the benchmark in DBD LT.[18] However, the graft utilization rate was significantly higher in the HOPE group, despite longer donor warm ischemic times and higher donor age, compared to liver grafts transplanted after NRP. After propensity

**TABLE 1.** Donor, Graft, and Preservation Characteristics

| | NRP n = 132 | HOPE n = 93 | *P*-value |
|---|---|---|---|
| Donor age, yr | 50 (39–59) | 61 (52–71) | **<0.001** |
| Donor BMI, kg/m$^2$ | 24 (22–27) | 26.1 (24–27.8) | **<0.001** |
| Cause of death, n (%) | | | |
| Cerebrovascular accident | 42 (31.8) | 28 (30.1) | 0.785 |
| Hypoxic brain injury | 57 (43.2) | 48 (51.6) | 0.212 |
| Trauma | 33 (25) | 17 (18.2) | 0.232 |
| Donor ICU stay, days | 9 (6–15.5) | 4 (3–7) | **<0.001** |
| Donor AST (IU) | 51 (31–79.5) | 68 (40–111) | **0.001** |
| Donor ALT (IU) | 42 (26.5–90.5) | 61 (29–94) | 0.276 |
| Donor GGT (IU) | 88 (41–191) | 62 (27–155) | **0.037** |
| Total donor warm Ischemia, min | 31 (26.5–36) | 35 (30–39) | **<0.001** |
| Functional donor Warm ischemia, min | 22 (19–26) | 31 (26–35) | **<0.001** |
| Asystolic donor Warm ischemia, min | 17 (15–20) | 19 (17–21) | **0.017** |
| Procurement team, n (%) | | | |
| Local | 81 (61.4) | 65 (69.9) | 0.187 |
| Regional | 51 (35.1) | 28 (30.1) | 0.187 |
| NRP duration, min | 184 (159–207) | — | — |
| Static cold storage, h | 5.7 (4.7–6.6) | 4 (3.1–5) | **<0.001** |
| HOPE duration, min | — | 132 (105–165) | — |
| Total ex-vivo preservation, h | 5.7 (4.7–6.6) | 6.4 (5.6–7.4) | **<0.001** |
| Cold storage solution, n (%) | | | |
| IGL-1 | 96 (72.7) | 93 (100) | **<0.001** |
| Scot 15 | 34 (25.7) | 0 (0) | **<0.001** |
| Custodiol | 2 (1.5) | 0 (0) | **<0.001** |

Categorical variables are expressed in quantities and percentages and continuous variables are expressed as median with interquartile range.
BMI indicates body mass index; HOPE, hypothermic oxygenated perfusion; ICU, intensive care unit; IGL-1, Institute-George-Lopez-1; NRP, normothermic regional perfusion.

**TABLE 2.** Recipient Characteristics

| | NRP n = 132 | HOPE n = 93 | *P*-value |
|---|---|---|---|
| Recipient age, yr | 59.5 (54.5–63) | 59 (54–63.6) | 0.424 |
| Recipient BMI, kg/m$^2$ | 27.1 (24–30) | 27.5 (24.4–30) | 0.907 |
| Previous major surgery, n (%) | 26 (19.7) | 18 (19.4) | 0.949 |
| Indication for transplantaion, n (%) * | | | |
| Hepatitis B | 12 (9.1) | 8 (8.6) | 0.899 |
| Hepatitis C | 29 (22) | 31 (33.3) | 0.580 |
| Hepatitis C + B | 4 (3) | 2 (2.2) | 0.687 |
| Non-alcoholic-Steatohepatitis | 16 (12.1) | 11 (11.8) | 0.947 |
| Alcohol related liver disease | 53 (40.2) | 26 (28) | 0.059 |
| NASH + alcohol | 19 (14.4) | 5 (5.4) | **0.031** |
| Primary sclerosing cholangitis | 0 (0) | 1 (1.1) | 0.232 |
| Autoimmune Hepatitis | 3 (2.3) | 1 (1.1) | 0.503 |
| Hemochromatosis | 7 (5.3) | 0 (0) | **0.024** |
| Retransplantation | 0 (0) | 3 (3.2) | **0.038** |
| Other | 1 (0.8) | 0 (0) | 0.403 |
| Hepatocelluclar carcinoma, n (%) | 81 (54.7) | 67 (45.3) | 0.960 |
| Recipient pre-LT status, n (%) | | | |
| Home | 125 (94.7) | 83 (89.2) | 0.128 |
| In-hospital | 6 (4.5) | 9 (9.7) | 0.129 |
| Intubated | 1 (0.8) | 1 (1.1) | 0.803 |
| Pre-LT renal replacement therapy, n (%) | 3 (2.6) | 6 (6.5) | 0.171 |
| LabMELD score, points | 12 (8–16) | 12 (9–16) | 0.833 |
| DRI, points | 2.01 (1.75–2.31) | 2.47 (2.08–2.80) | **<0.001** |
| UK DCD-RISK score, points | 6 (3–8) | 9 (7–11) | **<0.001** |
| Low risk, n (%) | 64 (48.5) | 6 (6.5) | **<0.001** |
| High-risk, n (%) | 56 (42.4) | 45 (48.5) | 0.376 |
| Futile, n (%) | 12 (9.1) | 42 (45.2) | **<0.001** |

Categorical variables are expressed in quantities and percentages and continuous variables are expressed as median with interquartile range.
*One patient may present a combination of indications.
BMI indicates body mass index; DRI, donor risk index; LT, liver transplantation.

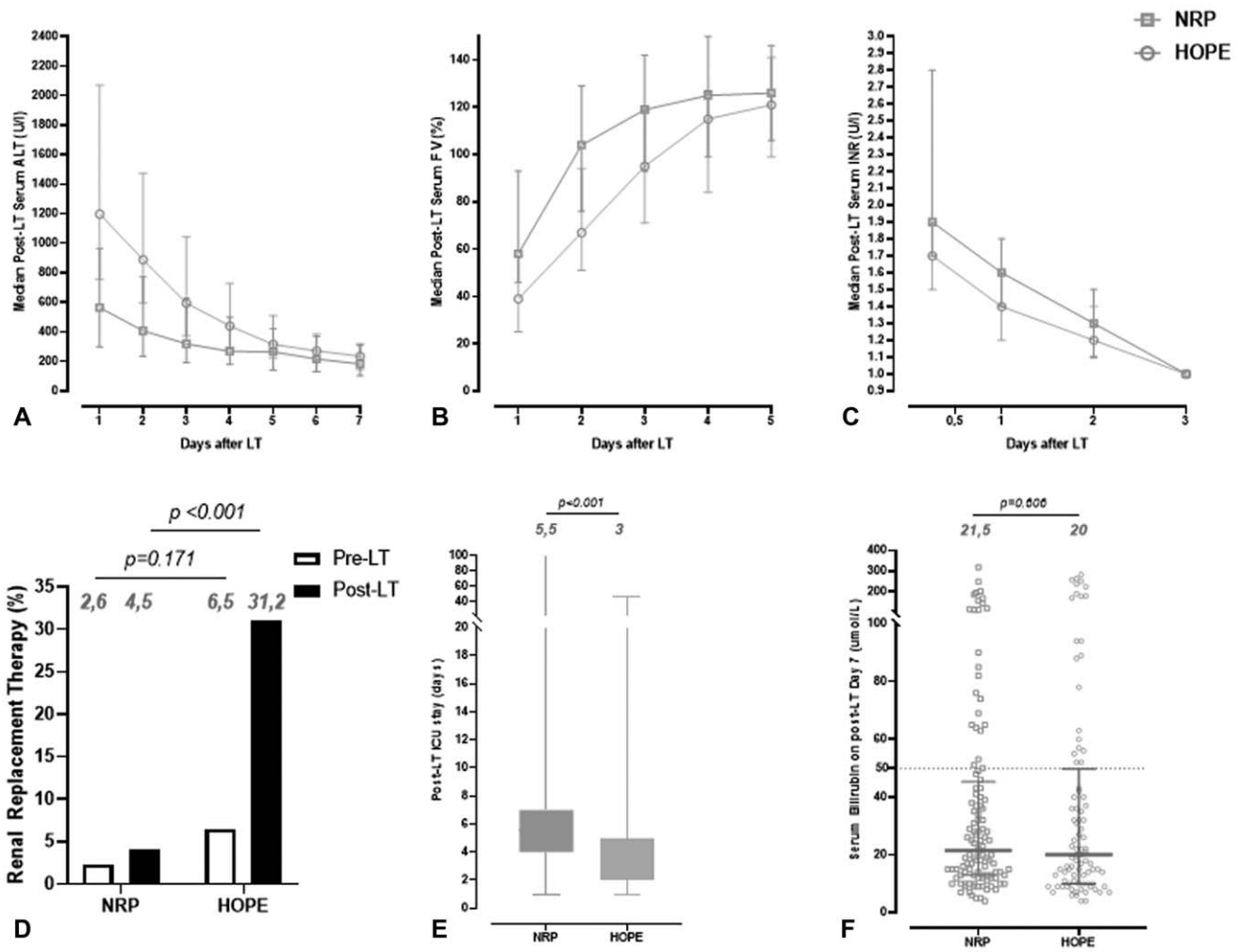
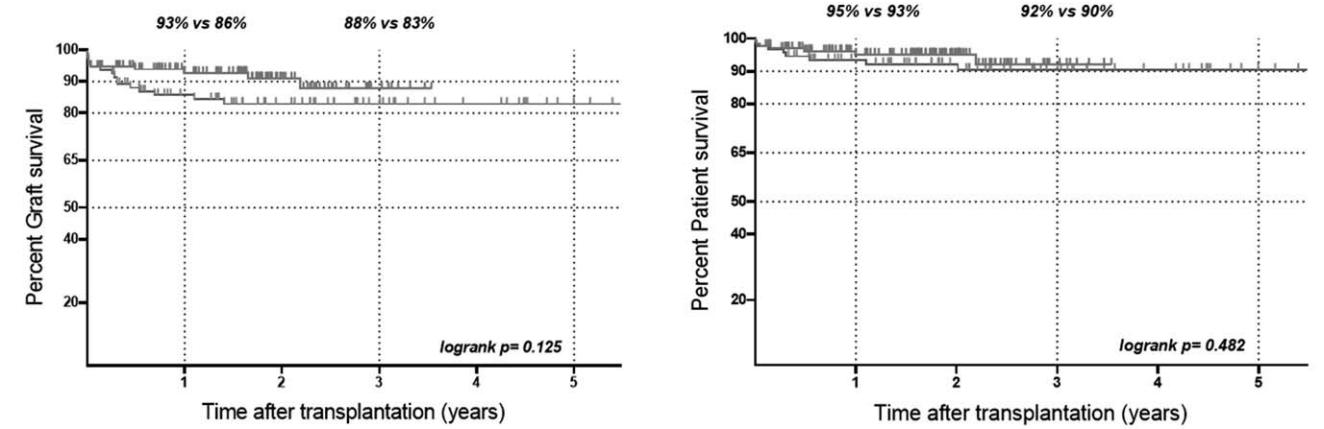



**FIGURE 2.** Early graft function and injury markers. A, Post-LT serum ALT release over the first 7 d. Early graft function expressed by Factor V (B) and INR (C). D, Pre- and Post-LT renal replacement therapy rates. E, ICU stay in days. F, Serum bilirubin on post-LT day 7. ICU indicates intensive care unit; LT, liver transplantation.




| | | | | | | |
|---|---|---|---|---|---|---|
| NRP | 132 | 82 | 33 | 8 | 0 | 0 |
| HOPE | 93 | 67 | 48 | 33 | 24 | 14 |

| | | | | | | |
|---|---|---|---|---|---|---|
| NRP | 132 | 91 | 41 | 8 | 0 | 0 |
| HOPE | 93 | 74 | 54 | 36 | 26 | 15 |

**FIGURE 3.** Tumor death censored graft and patient survival.

**TABLE 3.** Post-Transplant Outcomes in the Total and Propensity Score Matched Cohorts

| | NRP n = 132 | HOPE n = 93 | *P* value | PSM NRP$^X$ n = 32 | PSM HOPE$^X$ n = 32 | *P* value |
|---|---|---|---|---|---|---|
| ICU stay, days | 5.5 (4–7) | 3 (2–5) | <0.001 | 6 (4–10) | 3 (2–6) | 0.010 |
| Hospital stay, days | 17 (13–24) | 17 (13–23) | 0.510 | 18 (13–32) | 15 (10–25) | 0.513 |
| Serum Creatinine day 7 | 68 (58–90) | 127 (76–233) | <0.001 | 68 (57–101) | 111 (69–214) | 0.012 |
| Renal Replacement Therapy, n (%) | 6 (4.5) | 29 (31.2) | <0.001 | 4 (12.5) | 11 (34.4) | 0.092 |
| Biliary Complication, n (%) | 23 (17.4) | 32 (34.4) | 0.004 | 8 (25) | 11 (34.4) | 0.508 |
| Anastomotic Strictures, n (%) | 14 (10.6) | 24 (25.8) | 0.003 | 4 (12.5) | 7 (21.9) | 0.453 |
| Non-Anastomotic Strictures, n (%) | 6 (4.5) | 8 (8.6) | 0.215 | 2 (6.3) | 4 (12.5) | 0.688 |
| Billiary Leak, n (%) | 9 (6.8) | 6 (6.5) | 0.914 | 4 (12.5) | 2 (6.3) | 0.687 |
| Overall Arterial Complications, n (%) | 13 (9.8) | 7 (7.5) | 0.547 | 3 (9.4) | 2 (6.3) | 1 |
| Thrombosis, n (%) | 4 (3.0) | 2 (2.2) | 0.687 | 1 (3.1) | 0 (0) | 1 |
| Stenosis, n (%) | 8 (6.1) | 5 (5.4) | 0.829 | 2 (6.3) | 2 (6.3) | 1 |
| Primary-Non-Function (PNF), n (%) | 3 (2.3) | 4 (4.3) | 0.388 | 1 (3.1) | 3 (9.4) | 0.500 |
| Overall Graft Loss, n (%) | 18 (13.6) | 24 (25.8) | 0.021 | 5 (15.6) | 8 (25) | 0.727 |
| Tumor-Death Censored Graft Loss, n (%) | 10 (7.5) | 14 (15.1) | 0.075 | 4 (12.5) | 5 (16.5) | 1 |
| *Cause of Graft Loss, n (%)* | | | | | | |
| PNF | 3 (3.8) | 4 (4.3) | | 1 (3.1) | 3 (9.4) | |
| HAT | 0 (0) | 2 (2) | | 0 (0) | 0 (0) | |
| NAS | 1 (0.8) | 2 (2) | | 1 (3.1) | 0 (0) | |
| Septic Shock | 1 (0.8) | 2 (2) | | 1 (3.1) | 0 (0) | |
| Acute/Chronic Rejection | 1 (0.8) | 1 (1.1) | | 0 (0) | 0 (0) | |
| Arterial Stenosis | 0 (0) | 1 (1.1) | | 0 (0) | 1 (3.1) | |
| Tumor Recurrence | 6 (4.5) | 3 (3.2) | | 1 (3.1) | 2 (6.3) | |
| Secondary Tumor | 1 (0.8) | 5 (5.5) | | 0 (0) | 1 (3.1) | |
| Invasive Aspergillosis | 0 (0) | 1 (1.1) | | 0 (0) | 0 (0) | |
| Budd Chiari | 1 (0.8) | 1 (1.1) | | 0 (0) | 1 (3.1) | |
| Per-operative death | 1 (0.8) | 0 (0) | | 0 (0) | 0 (0) | |
| Gas embolism | 1 (0.8) | 0 (0) | | 0 (0) | 0 (0) | |
| Portal thrombosis | 1 (0.8) | 0 (0) | | 1 (0.8) | 0 (0.0) | |
| Unknown | 1 (0.8) | 2 (2) | | 0 (0) | 0 (0) | |

Categorical variables are expressed in quantities and percentages and continuous variables are expressed as median with interquartile range.
*X*: Propensity score matched cohorts.
HAT indicates hepatic artery thrombosis; ICU, intensive care unit; NAS, non-anastomotic biliary stricture; PNF, primary non-function.

score adjustment of donor-recipient combinations (median UK-DCD score 8), both strategies achieved similar post-LT outcomes.

Although static cold storage is still the gold standard in LT of low-risk DBD grafts, extended criteria grafts including cDCD may benefit from dynamic preservation strategies.[18–21] However, no direct comparison of such preservation strategies is currently available, making consensual conclusions impossible. Accordingly, this study aimed at providing a first comparison of NRP and HOPE in the setting of cDCD LT.

This is the largest series to date of NRP in cDCD LT. In 7 recently published studies including 8–95 patients, fDWI ranged from 10 to 28 minutes and donor age was <60 years (Supplementary Material, Fig. S5, http://links.lww.com/SLA/C422).[8,20,22–26] Outcomes in terms of graft and patient survival, PNF and NAS reported in this study are similar to the 95 NRP cases published by Hessheimer et al.[8] Of note, the Spanish series had a majority of pre-mortem cannulation with consequently shorter warm ischemic times.

In the direct comparison between HOPE and NRP, we observed a higher rate of EAD due to higher post-LT AST/ALT levels and a higher proportion of post-LT renal replacement therapy in the HOPE cohort. These differences did however not significantly impair early graft function nor reduce 1-year graft- and patient survival. The discrepancy between rates of EAD and post-LT liver function measured by INR and Factor V observed in the HOPE cohort warrants to review the current definition of EAD in the context of machine perfused cDCD grafts.[19,27] The higher post-LT renal replacement rate in the HOPE cohort may be partly explained by a 2× higher pre-LT renal replacement rate and the higher post-LT ALT/AST levels due to longer warm ischemia times.[28,29] Of note, after adjusting for donor-recipient risk combinations in the propensity score analysis, rates of renal replacement therapy were not significantly different between the 2 groups.

The ethical and regulatory issues surrounding the therapy withdrawal in the donor lead to specific modalities of organ procurement in the setting of cDCD. In Switzerland for example, placing catheters or administering heparinization before death of the donor is prohibited. This led to differences in the application of HOPE or NRP in the context of cDCD.

First, HOPE is an intervention on the liver graft after transport to the transplant center with standard static cold storage (end-ischemic ex-vivo perfusion). In contrast, NRP is an intervention in the donor, performed by the procurement team, with the need of static cold storage for transport to the transplant center.

Second, NRP requires preliminary vessel cannulation in the donor which is an additional technical challenge to the cDCD process.[30] Indeed, during the study period, 8% of cDCD procurements were aborted as a result of a technical problem with the NRP set-up. Of note, this observation should be interpreted in the context of an ongoing learning curve with NRP in some of the French centers, given the recent implementation of the procedure (2015). In contrast, no technical adverse event occurred during the 93 HOPE procedures. Although technical problems potentially occur with every perfusion technique, HOPE has the advantage to keep liver grafts at 8–10°C. In

contrast to normothermic temperatures, this significantly reduces the risk of organ damage if perfusion problems occur.[2]

Third, the duration of ex-vivo liver graft preservation, from aortic cross clamp in the donor to graft reperfusion in the recipient, was longer in the HOPE cohort without significantly increasing the duration of static cold storage. Because static cold storage negatively impacts post-LT outcomes, the possibility of end-ischemic ex-vivo perfusion may provide an advantage for HOPE in the setting of marginal cDCD grafts, re-allocation or difficult recipient hepatectomy by reducing cold ischemia of the liver graft.[31]

Another notable difference is the assessment of liver graft quality during preservation to safely increase utilization rates without compromising post-LT outcomes.[32] In the setting of NRP, some authors have suggested to use ALT/AST release and lactate clearance during perfusion as an indicator for graft quality.[20] Indeed, in this study, 5% of the cDCD liver grafts were discarded because AST/ALT levels rose to >4× baseline during NRP. Although transaminase release is a hepatocyte injury marker, it does not reflect bile duct viability or liver function and there's is no robust data from preclinical or human studies correlating AST/ALT to graft loss.[20,33–34] Finally, a potential advantage of NRP for organ assessment may be the ability to perfuse several cDCD organs at once including for example kidney, pancreas, and even lungs.[22] HOPE allows for a liver targeted metabolic assessment after the first 30 minutes of perfusion, based on a real-time measurement of perfusate levels of flavin mononucleotide (FMN), a fragment of complex I of the mitochondrial respiratory chain. FMN correlates with early graft function after transplantation in both DBD and cDCD.[16] In the HOPE cohort reported here, real-time FMN detection led to a cDCD graft utilization rate of 81%, in contrast to 63% by NRP, with tumor-censored graft survival comparable to DBD LT.

This study has several limitations. Data was gathered retrospectively from centers which use different cold storage solutions, transplantation techniques for example piggy-back versus classic technique, immunosuppression protocols and treatment modalities of biliary and arterial complications. In addition, donor selection was very different in both groups and may lead to biases and the study did not aim to assess oncological outcomes in cDCD recipients with HCC. Finally, cost assessment could not be performed due to the multicentric design and important health-care differences between the 2 countries.

In conclusion, NRP and HOPE in cDCD LT achieved similar tumor-death censored graft and patient survival rates. Yet, fewer grafts in the HOPE cohort were discarded, despite being procured from older donors with longer warm ischemia times. Thus, in contrast to some recent statements on the supremacy of NRP in cDCD, the presented data advocates the need for a well-designed randomized controlled trial, with an intention to treat analysis of outcomes after HOPE and NRP, specifically in high risk recipient-graft combinations.[35,36]

## ACKNOWLEDGMENTS

*The authors would like to thank all transplant coordinators and specialist nurses for their support and great effort in the respective cDCD programs.*

## REFERENCES

1. Merion RM, Pelletier SJ, Goodrich N, et al. Donation after cardiac death as a strategy to increase deceased donor liver availability. *Ann Surg*. 2006;244:555–562.
2. Martin JL, Costa ASH, Gruszcyk AV, et al. Succinate accumulation drives ischmeia-reperfusion injury during organ transplantation. *Nat Metab*. 2019;1:966–974.
3. Couchani ET, Pell VR, Gaude E, et al. Ischaemic accumulation of succinate controls reperfusion injury through mitochondrial ROS. *Nature*. 2014;515:431–435.
4. Blok JJ, Detry O, Putter H, et al. Longterm results of liver transplantation from donation after circulatory death. *Liver Transpl*. 2016;22:1107–1114.
5. Schlegel A, Kalisvaart M, Scalera I, et al. The UK DCD risk score: a new proposal to define futility in donation-after-circulatory-death liver transplantation. *J Hepatol*. 2018;68:456–464.
6. Coffey JC, Wanis KN, Monbaliu D, et al. The influence of functional warm ischemia time on DCD liver transplant recipients' outcomes. *Clin Transplant*. 2017;31. doi:10.1111/ctr.13068.
7. Monbaliu D, Pirenne J, Talbot D. Liver transplantation using donation after cardiac death donors. *J Hepatol*. 2012;56:474–485.
8. Hessheimer AJ, Coll E, Torres F. Normothermic regional perfusion vs. super-rapid recovery in controlled donation after circulatory death liver transplantation. *J Hepatol*. 2019;70:658–665.
9. Fondevilla C, Hessheimer AJ, Maathuis MH. Superior preservation of DCD livers with continuous normothermic perfusion. *Ann Surg*. 2011;254:1000–1007.
10. Dutkowski P, Schlegel A, De Oliveira M, et al. HOPE for human liver grafts obtained from donors after cardiac death. *J Hepatol*. 2014;60:765–772.
11. Muller X, Schlegel A, Würdinger M, et al. Can hypothermic oxygenated perfusion (HOPE) rescue futile DCD liver grafts? *HPB*. 2019;21:1156–1165.
12. Antoine C, Bronchard R, Durin L. Conditions à respecter pour réaliser des prélèvements d'organes sur donneurs décédés après arrêt circulatoire de la catégorie III de Maastricht dans un établissement de santé. Novembre 2019. Available at: https://www.agence-biomedecine.fr/IMG/pdf/v7_guide_ddac_-miii_novembre_2019.pdf. Accessed May 19, 2020.
13. Mohkam K, Dorez D, Mabrut JY. Liver transplantation from donors after circulatory death following the withdrawal of life-sustaining therapies: An answer to the shortage of grafts? *J Visc Surg*. 2016;153:325–326.
14. Kron P, Schlegel A, Mancina L, et al. Hypothermic oxygenated perfusion (HOPE) for fatty liver grafts in rats and humans. *J Hepatol*. 2018;68:82–91.
15. Schlegel A, Kron P, Graf R, et al. Warm vs. cold perfusion techniques to rescue rodent liver grafts. *J Hepatol*. 2014;61:1267–1275.
16. Muller X, Schlegel A, Kron P, et al. Novel real time prediction of liver graft function during hypothermic oxygenated machine perfusion prior to liver transplantation. *Ann Surg*. 2019;270:783–790.
17. Olthoff KM, Kulik L, Samstein B, et al. Validation of a current definition of early allograft dysfunction in liver transplant recipients and analysis of risk factors. *Liver Transpl*. 2010;16:943–949.
18. Muller X, Marcon F, Sapisochin G, et al. Defining benchmarks in liver transplantation: a multicenter outcome analysis determining best achievable results. *Ann Surg*. 2018;267:419–425.
19. Dutkowski P, Guarrera JV, de Jonge J, et al. Evolving trends in machine perfusion for liver transplantation. *Gastroenterology*. 2019;156:1542–1547.
20. Watson CJE, Hunt F, Messer S, et al. In situ normothermic perfusion of livers in controlled circulatory death donation may prevent ischemic cholangiopathy and improve graft survival. *Am J Transplant*. 2019;19:1745–1758.
21. Van Leeuwen OB, de Vries Y, Fujiyoshi M, et al. Transplantation of high-risk donor livers after ex situ resuscitation and assessment using combined hypo- and normothermic machine perfusion: a prospective clinical trial. *Ann Surg*. 2019;270:906–914.
22. Oniscu GC, Randle LV, Muiesan P, et al. In situ normothermic regional perfusion for controlled donation after circulatory death—the United Kingdom experience. *Am J Transpl*. 2014;14:2846–2854.
23. Ruiz P, Gastaca M, Bustamante FJ, et al. Favorable outcomes after liver transplantation with normothermic regional perfusion from donors after circulatory death: a single-center experience. *Transplantation*. 2019;103:938–943.
24. Minambres E, Suberviola B, Dominguez-Gil B, et al. Improving the outcomes of organs obtained from controlled donation after circulatory death donors using abdominal normothermic regional perfusion. *Am J Transplant*. 2017;17:2165–2172.
25. Hagness M, Foss S, Sorensen DW, et al. Liver transplant after normothermic regional perfusion from controlled donors after circulatory death: the Norwegian experience. *Transplant Proc*. 2019;51:475–478.
26. Rodríguez-Sanjuán JC, Ruiz N, Miñambres E, et al. Liver transplant from controlled cardiac death donors using normothermic regional perfusion: comparison with liver transplants from brain dead donors. *Transplant Proc*. 2019;51:12–19.
27. Jochmans I, Monbaliu D, Pirenne J, et al. The beginning of an end point: peak AST in liver transplantation. *J Hepatol*. 2014;61:1186–1187.

28. Leithead JA, Rajoriya N, Gunson BK, et al. The evolving use of higher risk grafts is associated with an increased incidence of acute kidney injury after liver transplantation. *J Hepatol*. 2014;60:1180–1186.
29. Kalisvaart M, Schlegel A, Umbro I, et al. The impact of combined warm ischemia time on development of acute kidney injury in donation after circulatory death liver transplantation: stay within the golden hour. *Transplantation*. 2018;102:783–793.
30. Brogi E, Circelli A, Gamberini E, et al. Normothermic regional perfusion for controlled donation after circulatory death: a technical complication during normothermic regional perfusion. *ASAIO J*. 2020;66:e19–e21.
31. Karangwa S, Panayotova G, Dutkowski P, et al. Hypothermic machine perfusion in liver transplantation. *Int J Surg*. 2020. ISSN 1743-9191, https://doi.org/10.1016/j.ijsu.2020.04.057.
32. Watson CJE, Jochmans I. From ''gut feeling'' to objectivity: machine preservation of the liver as a tool to assess organ viability. *Curr Transplant Rep*. 2018;5:72–81.
33. Eshmuminov D, Becker D, Bautista Borrego L, et al. An integrated perfusion machinepreserves injured human livers for 1 week. *Nat Biotechnol*. 2020;38:189–198.
34. Peris A, Lazzeri C, Bonizzoli M, et al. A metabolic approach during normothermic regional perfusion in uncontrolled donors after circulatory death-A pilot study. *Clin Transplant*. 2018;32:e13387.
35. Ruiz P, Gastaca M, Bustamante FJ, et al. The authors' reply: to NRP or not to NRP, that is the question. . .. *Transplantation*. 2019;103:e400.
36. Ayorinde JOO, Webb GJ, Richards JA. To NRP or not to NRP, that is the question. . .. *Transplantation*. 2019;103:e399.