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THOUGHTS & PROGRESS

Hypothermic oxygenated machine perfusion for extended criteria donor allografts: Preliminary experience with extended organ preservation times in the setting of organ reallocation

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Abstract

Background: In times of critical organ shortage, poor organ pool utilization and increased use of extended-criteria donor (ECD) allografts remain a major problem. Hypothermic oxygenated machine perfusion (HOPE) has emerged as a promising and feasible strategy in ECD liver transplantation (LT). However, potential safety limits regarding the duration of perfusion are yet to be explored. Besides marginal allograft quality (steatosis), prolonged cold ischemia time remains the most important factor for a high number of liver allografts being declined for transplantation.

Patients and Methods: Two ECD-allografts were each allocated to two recipients, who proved to be unsuitable to receive the assigned allograft upon arrival at the transplant center. The organs were reallocated by Eurotransplant and accepted by our center for two different backup patients. During that time, HOPE was commenced and continued until the recipient hepatectomy was completed. Postoperative allograft function was assessed by serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, and International Normalized Ratio. Incidence of early allograft dysfunction (EAD), postoperative complications, and length of hospital stay were analyzed.

Results: HOPE was applied for 4 h 35 min and 4 h 20 min, resulting in a total cold preservation time of 17 h 29 min and 15 h 20 min, respectively. Both recipients displayed decreasing serum transaminases and bilirubin levels postoperatively.

Abbreviations: ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; BMI, body mass index; CCI, comprehensive complication index; CIT, cold ischemia time; DBD, donation after brain death; DCD, donation after circulatory death; EAD, early allograft dysfunction; ECD, extended criteria donor; ETDRI, eurotransplant donor-risk-index; GGT, gamma-glutamyltransferase; HCC, hepatocellular carcinoma; HOPE, hypothermic oxygenated machine perfusion; HTK, histidine tryptophan ketoglutarate; ICU, intensive care unit; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; NASH, non-alcoholic steatohepatitis; WIT, warm ischemia time.

No EAD or major postoperative complications occurred in either patient. Serum ALT and AST levels were within the normal range at discharge.

Conclusions: Extended HOPE enables the safe extension of preservation time for up to 18 h in human LT. End-ischemic HOPE may significantly improve organ pool utilization, while simultaneously facilitating operating room logistics and preventing organ injury.

KEYWORDS

donation after brain death, extended criteria donor, extended preservation time, hypothermic oxygenated machine perfusion, liver transplantation, operating room logistics

1 | INTRODUCTION

Liver transplantation (LT) remains the only curative treatment for patients with end-stage liver disease. While the demand for organ transplantation has increased over time, liver allografts that would have previously been deemed unsuitable for transplantation, due to their compromised quality, have nowadays become an essential part of the organ pool and are being routinely transplanted in extended criteria donor (ECD) programs. Compared to healthy allografts, ECD livers are more susceptible to ischemia-reperfusion injury and relevant impairment of allograft function upon prolonged cold ischemia time (CIT), and are, therefore, associated with a higher risk of postoperative complications.[1] In this context, machine perfusion (MP) of the explanted donor liver has been recognized as a promising strategy in ECD-LT.[2,3] So far, several preclinical and clinical studies have demonstrated the advantages of hypothermic oxygenated machine perfusion (HOPE).[4–7] Even though, two recently published randomized controlled trials provide for the first-time level I evidence that HOPE, in comparison to static cold storage, significantly reduces non-anastomotic biliary strictures and early allograft injury in donation after circulatory death (DCD) and ECD donation after brain death (DBD) LT, respectively,[8,9] potential safety limits and benefits of extended HOPE duration remain to be explored. Besides marginal allograft quality, prolonged CIT and organ logistics remain two of the most important factors for a high number of procured liver allografts being declined for transplantation. We here present the first two successful cases where extended HOPE was necessitated in ECD allografts due to organ reallocation, resulting in a total cold preservation time of up to 18 h.

2 | PATIENTS AND METHODS

Two ECD allografts from DBD were each allocated to two recipients at our center. The first allograft originated from a 50-year-old donor with hypoxic brain death after a drug overdose and cardiopulmonary resuscitation for over one hour. Alanine- (ALT) and aspartate aminotransferase (AST) were both above 1000 U/L. The allograft showed 5% macro- and 20% microvesicular steatosis, as well as grade I liver fibrosis. Upon arrival at our transplant center, CIT was 12 h and 8 min. The second allograft originated from a 68-year-old donor with a traumatic subdural hemorrhage. The donor had a history of chronic alcohol abuse, with chronic cholangitis, and chronic hepatitis B virus infection. The serum ALT and AST were within the normal range. The allograft had a 5% macro- and no microvesicular steatosis, and a grade II liver fibrosis. The CIT was 10 h and 50 min. Further information on donor characteristics is summarized in Table 1.

Upon the arrival at the transplant center, in each case the recipient to whom the allograft was originally allocated proved to be unsuitable to receive the assigned allograft. The first patient had a previously undetected pulmonary arterial hypertension (47 mm Hg) and was deemed unfit for operation and anesthesia. The second recipient was an overall high-risk patient (labMELD of 28) and was unsuitable to receive an allograft with grade II liver fibrosis. Therefore, both organs were reallocated by Eurotransplant and were finally accepted by our center for two different backup patients. This resulted in prolonged CIT in both cases, while waiting for the backup recipients to arrive. During that time, the allografts were submitted to HOPE. Both allografts were treated with HOPE after back table surgery until recipient hepatectomy was completed. HOPE was applied via the portal vein in a pressure-controlled CE-marked machine perfusion device (VitaSmart, Bridge to Life Ltd., Columbia, United States of America) with 2–5 mm Hg at 4–10°C with re-circulating oxygenated perfusate (Belzer UW-MPS, Bridge to Life Ltd., Columbia, United States of America). Before actual implantation, HOPE-treated allografts were again flushed with cold histidine tryptophan ketoglutarate (HTK) solution to wash out residual UW-MPS. LT was performed

TABLE 1 Demographic and clinical data of donors

	Donor 1	Donor 2
Age (years)	50	68
Sex	Female	Male
BMI (kg/m^2)	22	23
Cause of death	Anoxic brain damage	Traumatic subdural hemorrhage
ICU stay (days)	8	3
Risk factors	Cardiopulmonary resuscitation > 1 h	Past hepatitis B virus infection (HBcAb positive, HBsAg negative, HBsAb positive, HBV PCR negative) Morbus Whipple, Billroth-II gastrectomy with Roux-Y-Anastomosis due to gastric ulcer
AST peak (U/L)	1663	23
ALT peak (U/L)	2185	14
Bilirubin peak (μmol/L)	6.8	5.8
Liver histology	Microvesicular steatosis 0%–5%; macrovesicular steatosis 20%; slight portal fibrosis	Microvesicular steatosis 0%–5%; macrovesicular steatosis 0%; portal fibrosis with infrequent septa (stage F2)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B Virus; ICU, intensive care unit; PCR, polymerase chain reaction.

using the classic total vena cava replacement technique with a side-to-side choledochocholedochostomy as previously described.[10]

3 | RESULTS

The first allograft underwent HOPE for 4 h and 35 min, resulting in a total cold preservation time of 17 h and 29 min. Recipient 1 (R1) was a 56-year-old male with nonalcoholic steatohepatitis (NASH)-associated hepatocellular carcinoma (HCC) within Milan criteria and a labMELD of 11. The second allograft underwent 4 h and 20 min of HOPE and was transplanted to a 55-year-old male recipient (R2) with HCC outside the Milan criteria and a labMELD of 10. Total cold preservation time was 15 h and 20 min.

Both recipients displayed decreasing serum transaminases and bilirubin levels postoperatively (Figure 1). The calculated early allograft failure simplified estimation (EASE) score was −4.5 for R1 and −2.6 for R2, categorizing the recipients in an extremely low risk and low-risk class for early allograft failure, respectively.[11] Indeed, no early allograft dysfunction (EAD) or graft failure occurred in either patient. While the first patient had a rather uneventful postoperative course, the second patient suffered pronounced postoperative delirium, with hyperammonemia and decreased vigilance. He, therefore, underwent five days of continuous venovenous hemofiltration for ammonia clearance. The renal function was not impaired at any time. Furthermore, he suffered from a mild rejection on postoperative day 10, which was successfully treated with 500 mg methylprednisolone for three consecutive days. Moreover, R2 necessitated paracentesis on postoperative day 21 due to refractory ascites, after the removal of the intraoperatively placed abdominal drainage. In both patients, biliary drainage (T-Drainage) that is routinely used in our center, was visualized by contrast-enhanced x-ray on postoperative day 5 and could be removed 6 weeks after surgery. There were no major postoperative complications as assessed by the Clavien-Dindo classification. The hospital stay was 14 days (R1) and 30 days (R2), respectively. Serum ALT (R1 28 U/L and R2 13 U/L) and AST (R1 32 U/L and R2 20 U/L) levels were within the normal range on the day of discharge. At the one-year follow-up, both patients presented in a good general condition, with liver enzymes, bilirubin, and coagulation parameters being in a normal range. Moreover, both had an uneventful course after being discharged from the hospital, without any additional postoperative complications occurring until the present date. Detailed data on recipient characteristics including comorbidities are found in Table 2.

4 | DISCUSSION

Despite the significant progress of machine perfusion, prolonged CIT, and operating room logistics remain a persisting obstacle and the cause for a high number of liver allografts being declined for transplantation. Herein, we demonstrate the successful use of HOPE in a so-far unexplored clinical setting. Two ECD allografts from DBD donors underwent HOPE to extend the preservation time and bridge the time gap until the arrival of the allocated backup recipients. Preservation with HOPE reduces

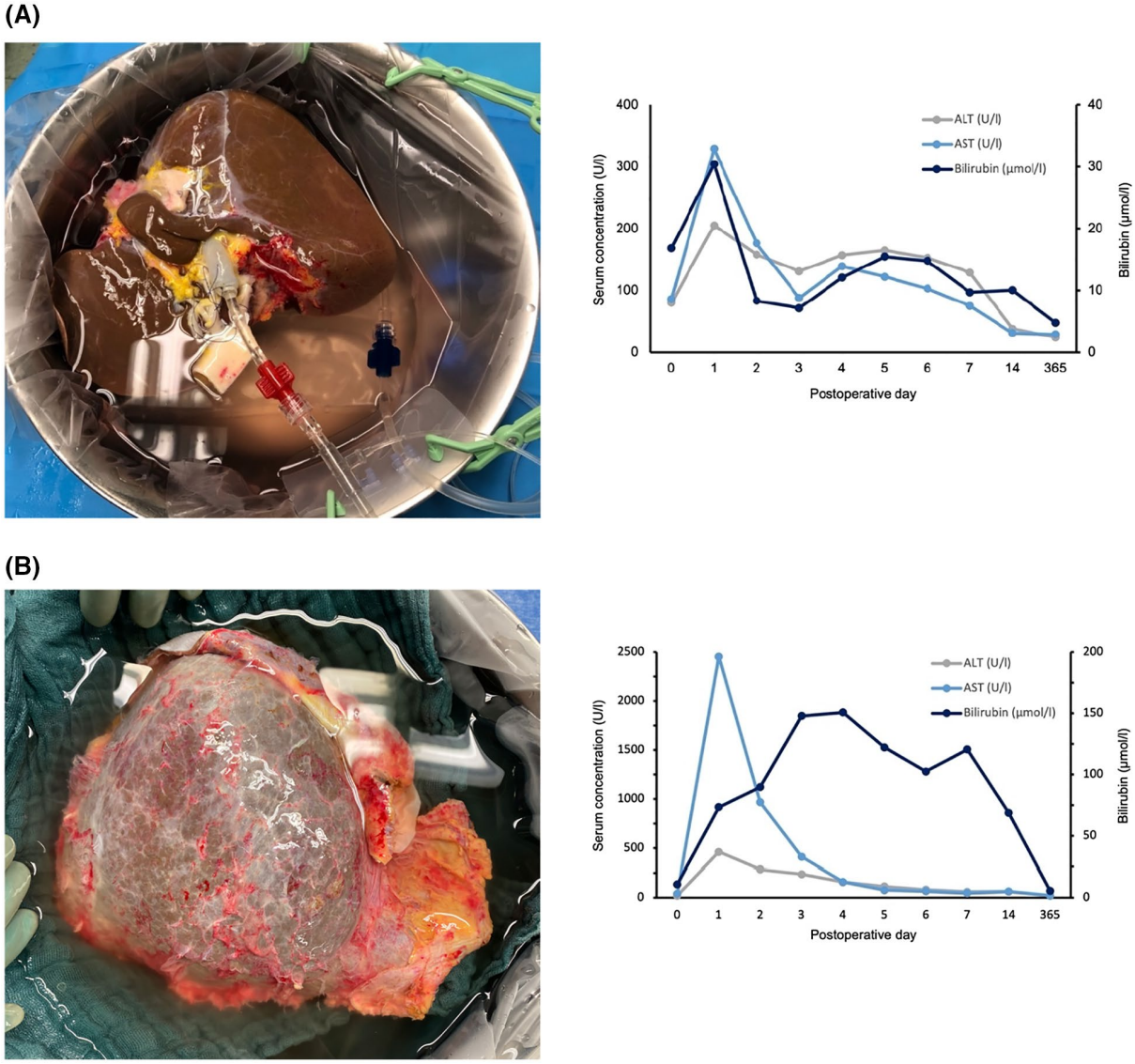

FIGURE 1 Intraoperative photos of liver from donor 1 (A) and donor 2 (B) with time course of serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin levels of both recipient 1 (A) and recipient 2 (B) during the first 14 postoperative days and at one year after liver transplantation [Color figure can be viewed at wileyonlinelibrary.com]

reactive oxygen species production and alleviates ischemic reperfusion injury, thus stabilizing postoperative liver function.[9,12,13] Most studies currently apply HOPE for 1–2 h, whereas significantly longer perfusion times were mainly described in vitro or in animal models.[14,15] A recent study by the Groningen group reported successful preservation with HOPE for 24 h in a porcine model. No increase in hepatocellular or biliary injury was observed when compared to shorter preservation times, whereas livers preserved by 24 h of static cold storage were non-functioning.[16] In line with those findings, a group from Milan reported two cases, where the cold preservation time of liver allografts was extended to 20 h by applying HOPE for up to 8 h, nonetheless resulting in excellent functional graft recovery.[17] Remarkably, donor allografts used in these cases were both of excellent quality. Even though prolonged dynamic preservation times with HOPE were recently described,[18] the here reported clinical cases are the first to demonstrate the safety and feasibility of extended static and dynamic preservation of ECD organs with HOPE for up to 18 h in the clinical setting of organ reallocation and operating room logistics. Both allografts displayed good graft function and no EAD postoperatively.

The possibility of performing LT without limitations due to CIT might redefine multiple aspects of current LT practice. Safe prolongation of organ perseveration times could render the shift of night-time transplantations into daytime procedures possible, thus reducing the perioperative stress of a night-time emergency case. Indeed, the current literature shows no significant difference between day- and night-time LT in terms of postoperative graft- and patient survival, or postoperative complications requiring

TABLE 2 Demographic and clinical data of recipients

	Recipient 1	Recipient 2
Age (years)	56	55
Sex	Male	Male
BMI (kg/m^2)	35.4	25.4
Comorbidities	Esophageal varices I°, diabetes mellitus type 2	Esophageal varices I–II°, diabetes mellitus type 2, Heparin-induced thrombocytopenia type 2
Liver disease	NASH-associated HCC (within Milan criteria)	HCC in alcoholic cirrhosis (outside Milan criteria)
labMELD	11	10
ETDRI	2.28	2.38
WIT (min)	46	45
Total cold preservation time (h)	17:29	15:20
HOPE duration (h)	4:35	4:20
CCI	8.7	54.1
Duration ICU-stay (days)	7	25
Duration hospital-stay (days)	14	30

Abbreviations: BMI, body mass index; CCI, Comprehensive-Complication-Index; EDTRI, Eurotransplant Donor-Risk-Index; HCC, hepatocellular caricoma; HOPE, hypothermic oxygenated machine perfusion; ICU, intensive care unit; MELD, Model for End Stage Liver Disease; NASH, non-alcoholic steatohepatitis; WIT, warm ischemia time.

re-operation.[19,20] However, the effect of night-time operations on a surgeon and staff burnout should not be underestimated, especially in times of a limited pipeline of future transplant surgeons.[20] Remarkably, a recently completed randomized controlled trial by our group demonstrated a significant decrease in postoperative complication rates in HOPE-treated allografts, along with lower overall procedural costs compared to static cold storage, thus confirming that the benefits of HOPE aren't only limited to allograft and patient-related problems.[9] Extended cold preservation with HOPE may significantly improve organ pool utilization, while simultaneously facilitating operating room logistics and preventing organ injury. Validation in prospective clinical trials is warranted.

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CONFLICT OF INTEREST

The authors of this manuscript have no conflicts of interest.

AUTHOR CONTRIBUTIONS

The manuscript was drafted by Sandra Pavicevic and Georg Lurje Data collection, interpretation, and analysis were performed by Sandra Pavicevic and Georg Lurje Further authors (Deniz Uluk, Sophie Reichelt, Panagiotis Fikatas, Brigitta Globke, Nathanael Raschzok, Moritz Schmelzle, Robert Öllinger, Wenzel Schöning, Dennis Eurich, Johann Pratschke) have substantially contributed to the final version of the manuscript. All authors have read and approved the final version of the manuscript.

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