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Portable hypothermic oxygenated machine perfusion for organ preservation in liver transplantation: A randomized, open-label, clinical trial

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Abstract

Background and Aims: In liver transplantation, cold preservation induces ischemia, resulting in significant reperfusion injury. Hypothermic oxygenated machine perfusion (HMP-O_2) has shown benefits compared to static cold storage (SCS) by limiting ischemia-reperfusion injury. This study

Abbreviations: CIT, cold ischemia time; DCD, donation after cardiac death; D-HOPE, Dual-Hypothermic Oxygenated machine PErfusion; DSMB, Data Safety Monitoring Board; EAD, early allograft dysfunction; ECD, extended criteria donors; FDA, Food and Drug Administration; HA, hepatic artery; HAT, hepatic artery thrombosis; HMP, hypothermic machine perfusion; HMP-O_2, hypothermic oxygenated machine perfusion; IRB, Institutional Review Board; LLT, LifePort Liver Transporter; LOS, length of stay; LT, liver transplantation; mITT, modified intent-to-treat; OPO, organ procurement organization; PILOT, Perfusion to Improve Liver Outcomes in Transplantation; Plt, pooled platelets; PNF, primary nonfunction; PP, per-protocol; PV, portal vein; SAE, serious adverse event; SCS, static cold storage; UNOS, United Network of Organ Sharing; WIT, warm ischemia time.

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reports outcomes using a novel portable HMP-O_2 device in the first US randomized control trial.

Approach and Results: The PILOT trial (NCT03484455) was a multicenter, randomized, open-label, noninferiority trial, with participants randomized to HMP-O_2 or SCS. HMP-O_2 livers were preserved using the Lifeport Liver Transporter and Vasosol perfusion solution. The primary outcome was early allograft dysfunction. Noninferiority margin was 7.5%. From April 3, 2019, to July 12, 2022, 179 patients were randomized to HMP-O_2 (n = 90) or SCS (n = 89). The per-protocol cohort included 63 HMP-O_2 and 73 SCS. Early allograft dysfunction occurred in 11.1% HMP-O_2 (N = 7) and 16.4% SCS (N = 12). The risk difference between HMP-O_2 and SCS was −5.33% (one-sided 95% upper confidence limit of 5.81%), establishing noninferiority. The risk of graft failure as predicted by Liver Graft Assessment Following Transplant score at seven days (L-GrAFT$_7$) was lower with HMP-O_2 [median (IQR) 3.4% (2.4–6.5) vs. 4.5% (2.9–9.4), $p = 0.024$]. Primary nonfunction occurred in 2.2% of all SCS (n = 3, $p = 0.10$). Biliary strictures occurred in 16.4% SCS (n = 12) and 6.3% (n = 4) HMP-O_2 ($p = 0.18$). Nonanastomotic biliary strictures occurred only in SCS (n = 4).

Conclusions: HMP-O_2 demonstrates safety and noninferior efficacy for liver graft preservation in comparison to SCS. Early allograft failure by L-GrAFT$_7$ was lower in HMP-O_2, suggesting improved early clinical function. Recipients of HMP-O_2 livers also demonstrated a lower incidence of primary nonfunction and biliary strictures, although this difference did not reach significance.

INTRODUCTION

Liver transplantation (LT) remains the only effective treatment for end-tage liver disease; however, organ demand continues to exceed supply.[1] Extended criteria donor (ECD) grafts, [ie, advanced age, steatotic, and donation after cardiac death (DCD)] are frequently discarded. These are particularly sensitive to ischemia-reperfusion injury and risk poor patient outcomes.[2] Over the past decade, the prevelance of ECD grafts is rising due to increasing age and obesity.[3] Expanded ECD graft utilization could increase donor supply and alleviate demand gaps. Enhancing the liver's tolerance of ischemia-reperfusion injury through optimization of organ preservation may safely facilitate ECD graft utilization and improve patient access to LT.

Static cold storage (SCS), the current standard of care for liver graft preservation, exacerbates ischemic injury by storing livers in a hypoxic environment. We described a novel technique for fully portable hypothermic oxygenated machine perfusion (HMP-O_2).[4] This provides continuous circulation through the portal vein (PV) and hepatic artery (HA) utilizing oxygen-enriched preservation solution. HMP-O_2 mitigates ischemia-reperfusion injury by flushing toxins and maintaining low metabolic demand under hypothermic oxygenated conditions.[5] Ultimately, this protects mitochondria and prevents bioenergetic depletion.[6] As little as 60 minutes of oxygenated perfusion, even after a period of SCS, mitigates ischemic mitochondrial injury.[7] The biliary tree, which is especially vulnerable to ischemia, particularly benefits from HMP-O_2, resulting in reduced ischemic biliary complications.[8]

Hypothermic machine perfusion (HMP) as an alternative to SCS for organ preservation is well established in kidney transplantation and reduces delayed graft function.[9] Application of this technology to LT, however, has only recently gained considerable traction. Our team reported the first clinical series establishing the safety and feasibility of HMP in human LT in 2010.[10] Subsequently, we reported the first series utilizing HMP to preserve "orphan" ECD liver grafts (declined by other centers), demonstrating successful utilization and improved post-LT outcomes compared with similar grafts preserved by SCS.[11] Application to DCD grafts followed,[8,11] demonstrating decreased biliary complications and improved 1-year graft survival after HMP-O_2 in matched cohorts.[11,12]

Over the past 5 years, investigation of HMP-O_2 has progressed beyond the single-center and multicenter experiences.[5,11,13–15] Several European RCTs demonstrated decreased biliary complications,[8] early allograft dysfunction (EAD), length of stay (LOS),[16] and postoperative complications following HMP-O_2,[15] particularly for ECD grafts.[17–19] HMP-O_2 optimizes graft function and increases ECD utilization in European centers; however, to date, HMP-O_2 has yet to be widely adopted in the United States. The present study presents the outcomes from the first US RCT comparing HMP-O_2 to SCS using a fully portable HMP-O_2 device.

METHODS

Study design

The Perfusion to Improve Liver Outcomes in Transplantation (PILOT) trial (NCT03484455) was a multicenter, open-label, RCT to evaluate HMP-O_2 using the LifePort Liver Transporter (LLT) and Vasosol preservation solution (Organ Recovery Systems, Itasca, IL) compared with standard-of-care SCS for LT by noninferiority design. The study was conducted in compliance with U.S. Food and Drug Administration (FDA) regulations, guidelines for good clinical practice, and the ethical principles of the Declaration of Helsinki and Istanbul. Consent was provided in writIng for all subjects enrolled in the study. Institutional Review Board (IRB) approval was obtained through each individual center. Nine US LT centers were included as clinical sites (Supplemental Figure S1 http://links.lww.com/HEP/I161) and provided IRB approval, including Rutgers New Jersey Medical School/University Hospital (lead coordinating site), Columbia, Intermountain, Montefiore, Northwestern, and the Universities of Chicago, Cincinnati, Rochester, and Virginia.

Patients

Patients were recruited from April 3, 2019, to July 12, 2021, with data collection through July 12, 2022. Patients 18 years or above actively listed on the United Network of Organ Sharing (UNOS) waitlist for whole liver transplants were eligible. Recipient exclusion criteria included age below 18 years, multiorgan transplant, re-do LT, ABO incompatibility, severe systemic infection, HIV^+, acute/fulminant hepatic failure, and pregnancy. All whole donor liver offers were eligible for inclusion. Donor exclusion criteria included HIV^+ and anticipated cold ischemia time (CIT) <3 hours (Supplemental Figure S2, http://links.lww.com/HEP/I162). Sex/gender information was self-reported as biologic/physiologic sex traits assigned at birth as recorded by UNOS (male/female). Participants provided written and verbal consent for enrollment, and surrogate consent was allowable based on center protocol.

Randomization and masking

Patients who consented were sequentially randomized to SCS (control) or HMP-O_2 (intervention) at organ offer. Stratified randomization was performed by means of a password protected, computerized, automated model within the electronic data capture system (Medrio, San Francisco, CA). Patients were randomized based on DCD status (yes/no) and listed MELD-Na ($\leq 30/>30$) score. This yielded 4 independent randomization strata (DBD/MELD ≤ 30, DBD/MELD >30, DCD/MELD ≤ 30, DCD/MELD >30). Within each stratum, treatment assignment (HMP-O_2/SCS) was independently balanced. Neither the subject nor investigators were blinded (open-label design). Randomization was performed globally for all study participants rather than on a per-center basis and was balanced at randomization rather than enrollment. The study design is shown in Figure 1.

Procedures: machine perfusion and liver transplant

Donor livers randomized to HMP-O_2 were prepared, cannulated, and placed on the LLT by qualified site personnel. Donor liver perfusion was classified as delayed end-ischemic (ie, period of SCS prior to perfusion) or immediate post-procurement (ie, initiated at the donor hospital). Timing of HMP-O_2 was at site investigator discretion. Perfusion was performed through the HA and PV utilizing Vasosol, a proprietary preservation solution, as described.[5,10] Briefly, 3 L of chilled Vasosol was decanted into the perfusion circuit. Preoxygenation was performed through a device-specific closed-system chamber cover providing insufflation of 100% oxygen at 10 L/min for >20 minutes.[4] Preoxygenation results in an average dissolved preservation fluid oxygen content of 688.4 ± 43.9 mm Hg and corresponding liver tissue oxygen tension of 200.0 ± 0.0 mm Hg.[4] Perfusate oxygen levels were not assessed as part of the trial. Atraumatic HA and PV cannulas, specially designed for the LLT, were size matched to vascular inflow. Cannulated livers were then flushed with an additional 1 L of Vasosol prior to placement in the organ chamber and attachment of inflow tubing to the cannulas. Continuous, nonpulsatile, flow-controlled HA and PV perfusion was initiated, with target flow adjusted by graft weight to 0.66 mL/g liver/minute (Figure 2). Following preservation, the allograft was removed from the device and flushed with 1.5–2.0 L of cold albumin prior to implantation. LT was performed using standard techniques.

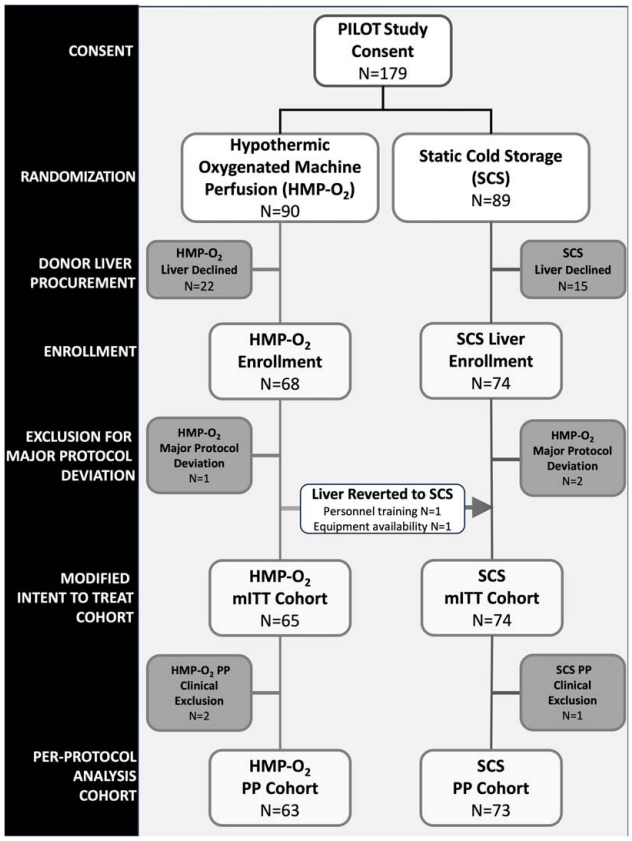

FIGURE 1 Clinical trial design and randomization. Enrollment, subject randomization design, and study inclusion for the modified intent-to-treat and per-protocol analysis cohorts. Abbreviations: HMP-O_2, hypothermic oxygenated machine perfusion; mITT, modified intent-to-treat; PILOT, Perfusion to Improve Liver Outcomes in Transplantation; PP, per-protocol; SCS, static cold storage.

Procedures: data collection and monitoring

Pre-LT data collected included donor and recipient parameters, as well as preservation details. Donor data included age, sex, ethnicity, comorbidities, peak and terminal liver function tests, cause of death, procurement location, DCD status, and height. Donor data were used to calculate the liver donor risk index.[20] Donor surgery data included cross-clamp time/date, *in situ* flush, arterial anatomy, and liver weight. For DCD donors, functional warm ischemia was recorded as time from extubation until initiation of cold *in situ* perfusion. Recipient data included age, sex, listing date, cause of end-stage liver disease, comorbidities, serologies, MELD-Na, pretransplant hospitalization, and labs <24 hours pretransplant. Liver allograft preservation data included duration of preservation. For HMP-O_2 grafts, additional data included preperfusion SCS duration, duration of preoxygenation, duration of perfusion, flow settings, serial perfusate temperature, HA and PV flows, and pressures. LT procedure data included total operative time and CIT, blood products, bile production, urine output, surgeon-reported reperfusion syndrome, and significant intraoperative events. Post-transplant data included lab data, recipient and graft status, complications, and physical exam for the first 7 days, as well as at 3-, 6-, and 12-months post-LT. All subjects were followed for at least 12 months post-LT. Protocol compliance and safety were monitored by study sponsor and an independent data safety monitoring board.

Outcomes

Protocol-defined primary study endpoint was the incidence of EAD, defined by the Olthoff criteria[21] as post-LT presence of total bilirubin ≥ 10 mg/dL at 7 days, international normalized ratio ≥ 1.6 at 7 days, and/or ALT/AST > 2000 IU/L within 7 days and > 24 hours post-reperfusion. Binary assessment of EAD was supplemented in *post hoc* analysis with the Liver Graft Assessment Following Transplant score based on the AUC of 7-day post-LT variables (L-GrAFT$_7$) including AST, international normalized ratio, total bilirubin, and platelet count. This model allows dynamic, continuous, multivariate estimation of the risk of allograft failure or recipient death at 3 months.[22,23] Both EAD and L-GrAFT$_7$ were centrally assessed. Protocol-defined secondary end points included (1) primary nonfunction (PNF; defined as fulfilling UNOS criteria for status 1A relisting[24] and resulting in retransplant or death), (2) acute kidney injury <7 days based on Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) criteria ($\geq$2x increase in creatinine or $> 50\%$ decrease in glomerular filtration rate),[25] and (3) post-LT graft failure (retransplant or death from graft failure), biliary complications, vascular complications [PVT, hepatic artery thrombosis (HAT)], or subject death. Additional exploratory outcomes included hospital and intensive care unit LOS, lactate clearance, and time to laboratory normalization. Assessment of ischemic preservation injury, postoperative bleeding, incisional hernia, adverse event (AE) and serious adverse event (SAE) analysis, ECD and EAD subgroup assessments, and L-GrAFT$_7$ analysis were *post hoc* analysis additions (Supplemental Material 1, http://links.lww.com/HEP/I163).

Postoperative AEs within 12 months included the following: infection was identified by positive cultures combined with clinical signs of infection and subdivided by category. Major bleeding was categorized as need for post-transplant transfusion, operative intervention, or other. EAD, acute kidney injury, PNF, and vascular complications were defined as above. Biliary complications were subcategorized as leak or stricture. Those occurring in presence of HAT were excluded as being a consequence of HAT ($n = 1$). Bile leak was diagnosed by biochemical or imaging evidence requiring intervention. Strictures were defined as endoscopic ductular narrowing with upstream dilation occurring at anastomosic or nonanastomotic locations. Early

FIGURE 2 Donor liver allograft perfusion with the Lifeport Liver Transporter portable hypothermic oxygenated machine perfusion device. (A) Following backtable preparation of the liver, atraumatic cannulas are inserted into the donor portal vein and hepatic artery. (B) Perfusion inflow tubing is connected to the portal vein and hepatic artery for continuous hypothermic infusion of Vasosol perfusion solution. (C) Representative photo of the device pump head and device display, which provides continuous information regarding line pressures, flow, and temperature during perfusion. (D) Representative photo of the closed device ready for transport of the donor liver.

post-transplant mechanical obstruction of the recipient duct due to blood clot (n = 1) or retained stone (n = 1) were excluded. Moderate to severe ischemic preservation injury was based on the presence of post-reperfusion syndrome as defined by Aggarwal et al[26] (mean arterial pressure decrease > 30% from baseline lasting > 1 minute following reperfusion) as reported by the operating surgeon and/or histologic evidence of moderate to severe preservation injury based on post-reperfusion biopsy evaluation by a blinded independent pathologist (Suzuki Assessment Score).[27] Rejection included acute cellular rejection meeting Banff criteria.[28] Graft failure was considered retransplant or recipient death due to graft failure. Incisional hernia was assessed by physical exam. All other complications were recorded and subdivided based on organ system affected. AE reports related to symptoms without discernable diagnosis were excluded. All AEs were further classified as mild, moderate, or severe by center investigators. SAEs were defined as those leading to subject death, life-threatening injury, permanent impairment, prolonged hospitalization, or requiring significant medical or surgical intervention.

Statistical analysis

The study sample size was calculated based on the primary end point, incidence of EAD, assuming an incidence of 15% with HMP-O_2 and 30% with SCS.[5,10] With noninferiority margin of 7.5%, a sample size of 65 subjects per group was determined sufficient to

demonstrate noninferiority of HMP-O_2 at 90% power and alpha = 0.05 while accounting for 10% subject attrition. Target randomization of 90 per group was expected to result in enrollment of at least 70 patients per group, accounting for dropout and organ decline on visualization.

The study clinicaltrials.gov registration number is NCT03484455. Intent-to-treat population was designated for safety analysis in the study protocol as all randomized and consented subjects for which the randomized preservation method was initiated. This was later modified to exclude major protocol violations based on study ineligibility or inability to perform primary efficacy assessment. In addition, 2 patients who reverted to SCS prior to therapy initiation were included in the modified intent-to-treat (mITT) cohort since these events were felt unrelated to therapy. Device efficacy analysis was performed based on the per-protocol (PP) population, which was defined as the mITT subset that completed primary evaluation and lacked protocol deviations or clinical confounding parameters. All AEs and SAEs were reviewed by an independent Data Safety Monitoring Board (DSMB). Main comparative analyses occurred between PP recipients of livers preserved by HMP-O_2 or SCS. Study primary end point was noninferiority of EAD on PP analysis. L-GrAFT$_7$ score, which was described following the development of the original statistical analysis plan, was employed in *post hoc* analysis to supplement assessment of early allograft function. Study protocol and statistical analysis plan are provided as Supplemental Material 1, http://links.lww.com/HEP/I163 and 2, http://links.lww.com/HEP/I164.

Descriptive data are reported as frequencies and percent for categorical variables and median (IQR) or 95% confidence interval (CI) for continuous variables. Data were assessed for normality and variance by means of Shapiro-Wilk and Levene tests, respectively. Differences across groups are compared using independent samples *t* test or two-sample Wilcoxon test, where appropriate. Multigroup comparisons were performed using ANOVA or Kruskal-Wallis tests. Categorical variables were compared using chi-squared or Fisher exact tests. Survival data are depicted using Kaplan-Meier methods with differences across groups compared using the log-rank test. Proportional hazards of graft failure were further evaluated using the Fine-Gray model and the Cause-specific hazards model, allowing calculation in a competing risk setting. All tests were two-sided. For noninferiority analysis, relative risk difference was calculated using the Newcombe method with continuity correction, and the one-sided 95% CI was reported. Analyses were performed on SAS v9.4 (Cary, NC), GraphPad v9.4 (Boston, MA), or JMP v14.3 (Cary, NC). $p < 0.05$ was considered significant.

DATA DEPOSITION

Study data, including deidentified, coded participant data and data dictionary, will be made available on request from the corresponding author following the completion of the continued access phase of the trial and FDA device approval for research purposes only and with a signed data access agreement.

RESULTS

From April 3, 2019, to July 12, 2021, 179 subjects were enrolled across 9 centers (HMP-O_2 = 90; SCS = 89), of which 142 proceeded to LT (HMP-O_2 = 68; SCS = 74, Figure 1). Reasons for organ decline (HMP-O_2 = 22, SCS = 15) were related to liver age/quality/injury (54.4%, n = 20), DCD failing to expire (18.9%, n = 7), recipient instability (18.9%, n = 7), and other (8.1%, n = 3). There was no difference in organ refusal codes between groups ($p = 0.65$). Two HMP-O_2 cases reverted to SCS after randomization but prior to transplant due to limitations in personnel training or equipment. Both were deemed unrelated to device function and were included in the mITT cohort based on the therapy received. Three patients were excluded due to major protocol deviations related to failure to meet study inclusion/exclusion criteria (n = 1 HMP-O_2) or failure to collect labs for primary efficacy assessment (n = 2 SCS). This resulted in a mITT cohort of 139 patients (HMP-O_2 = 65, SCS = 74). For PP analysis, 3 patients were excluded based on confounding clinical parameters agreed on by study investigators [pre-preservation biopsy with > 70% macrosteatosis (HMP-O_2 = 1, SCS = 1) and pre-implantation sepsis (HMP-O_2 = 1)]. This resulted in a PP analysis cohort 63 HMP-O_2 and 73 SCS (N = 136, Figure 1). Analysis in this manuscript focuses on device efficacy in the PP cohort. For reference, primary and secondary outcomes used for safety assessment in the mITT cohort are available in Supplemental Table S1, http://links.lww.com/HEP/I165.

Recipient characteristics were similar between groups (Table 1). Alcohol-associated liver disease, steatotic liver disease, and chronic viral hepatitis accounted for 81.0% HMP-O_2 (N = 51) and 89.0% SCS (N = 65). Median laboratory MELD-Na was 24.0 in HMP-O_2 and 22.0 in SCS. HCC incidence was not subject to matching but was incidentally lower in HMP-O_2. Majority of patients were hospitalized with similar pre-LT LOS. Donor characteristics (Table 2) were similar between groups, with the exception of liver donor risk index, which was higher in HMP-O_2 ($p = 0.042$). ECDs were used in 23.8% HMP-O_2 (N = 15) and 28.7% SCS (N = 21; $p = 0.51$), which included 15 DCD allografts (HMP-O_2 = 5, SCS = 10). For all DCDs, functional warm ischemia time was

TABLE 1 Baseline characteristics of the per-protocol study population

	HMP-O_2 N = 63	SCS N = 73
Recipient age, median (IQR)	55 (45, 62)	56 (46, 62)
Recipient biologic sex, n (%)		
Male	38 (60.4)	47 (64.4)
Female	25 (39.7)	26 (35.6)
Recipient race/ethnicity, N (%)		
White	44 (69.8)	53 (72.6)
Black	2 (3.2)	4 (5.5)
Hispanic	9 (14.3)	12 (16.4)
Asian or Pacific Islander	3 (4.8)	1 (1.4)
Other	5 (7.9)	3 (4.1)
Recipient BMI, median (IQR)	28.8 (25.0, 33.9)	29.1 (25.7, 33.4)
Recipient baseline labs, median (IQR)		
AST, IU/L	57.0 (67.2, 121.9)	53.0 (55.9, 117.9)
ALT, IU/L	28.0 (33.6, 58.7)	31.0 (32.4, 56.9)
T. Bili, mg/dL	5.4 (7.3, 13.1)	3.5 (6.6, 12.0)
INR	1.9 (1.9, 2.4)	1.7 (1.7, 2.2)
Serum Cr	1.2 (1.3, 1.8)	1.2 (1.2, 1.8)
Primary liver failure etiology		
ARLD	24 (38.1)	25 (34.2)
SLD	12 (19.0)	16 (21.9)
Chronic viral hepatitis	15 (23.8)	24 (32.9)
Metabolic/genetic	1 (1.6)	3 (4.1)
Biliary cirrhosis	9 (14.3)	4 (5.5)
Other	2 (3.2)	1 (1.4)
HCC, N (%)	8 (12.7)	22 (30.1)
List MELD-Na, median (IQR)	26.0 (23.0, 33.0)	25.0 (20.5, 34.0)
Laboratory MELD-Na, median (IQR)	24.0 (18.0, 33.0)	22.0 (14.5, 32.0)
Pre-LT Hospitalization, d, median (IQR)	2.0 (1.0, 6.0)	2.0 (1.0, 4.0)
Pre-LT ICU, d, median (IQR)	0.0 (0.0, 2.0)	0.0 (0.0, 1.5)

Note: Data are n (%), median (IQR) or n/N (%).
Abbreviations: ARLD, alcohol-associated liver disease; Cr, serum creatinine; ICU, intensive care unit; INR, international normalized ratio; LT, liver transplant; SLD, steatotic liver disease; T Bili, total bilirubin.

<30 minutes. There were no differences in pre-procurement liver function tests, with the exception of peak alkaline phosphatase ($p = 0.029$). For HMP-O_2 grafts, 42.9% (N = 27) were immediately placed on the pump, with 81.4% transported by air and 14.8% by ground. The remaining 57.1% underwent delayed end-ischemic HMP-O_2, with a median 4.1 hours SCS prior to perfusion. Median perfusion time was 2.8 hours, with total CIT being similar between groups. During LT, total operative time and transfusion requirements were similar between groups. No serious device-related adverse events or unanticipated adverse device effects were documented.

The primary binary endpoint of EAD occurred in 14.0% of patients (N = 19), including 11.1% HMP-O_2 (N = 7, RR 0.68, 95% CI: 0.28–1.56, $p = 0.37$) and 16.4% SCS (N = 12). The risk difference between HMP-O_2 and SCS was −5.33%, which was within the noninferiority margin of 7.5% (one-sided 95% upper confidence limit: 5.81%, Figure 3), confirming noninferiority. While binary EAD assessment failed to establish superiority, EAD was classified as severe in 4/12 SCS, while no HMP-O_2 recipients developed severe EAD. To obtain more dynamic assessment of graft function, L-GrAFT$_7$ score was calculated to provide estimation of the 3-month risk of graft failure based on continuous longitudinal assessment of early allograft function. Median risk of graft failure by L-GrAFT$_7$ was significantly lower following HMP-O_2 (3.4%) compared to SCS (4.5%, $p = 0.024$).

Subgroup analysis assessing risk of EAD in ECD recipients was next performed. Of 36 ECD recipients, EAD occurred in 20.0% HMP-O_2 (N = 3/15, RR 0.60, 95% CI 0.19–1.76, $p = 0.0047$) compared with 33.3% SCS (N = 7/21). The risk difference for ECD recipients was −13.3% (one-sided 95% upper confidence limit 16.4%) (Figure 3). While the upper confidence limit exceeded the non-inferiority margin, preventing confirmation of subgroup non-inferiority, the point estimate of −13.3% suggests that HMP-O_2 may be beneficial in ECD recipients. Median L-GrAFT$_7$ score was similarly numerically lower but not statistically different for HMP-O_2 ECD recipients (2.9%, IQR 2.4–4.5) compared with SCS (4.3%, IQR 2.9–9.6, $p = 0.089$).

Secondary outcomes are presented in Table 3. While none reached statistical significance, there were some quantifiable trends. PNF occurred exclusively within SCS recipients (4.1%, N = 3, $p = 0.10$). Of these, 2 received retransplant and 1 expired due to graft failure. Graft failure requiring retransplant occurred in an additional 2 SCS recipients due to ischemic cholangiopathy (6.8% liver-related graft failure, N = 5). In contrast, only 1 HMP-O_2 recipient received retransplant because of HAT (1.6% liver-related graft failure, N = 1, $p = 0.14$). There was no difference in overall graft and patient survival between groups (Figure 4). One-year graft failure was further evaluated by competing risk assessment. HR for graft failure in HMP-O_2 compared with SCS was 0.228 (95% CI: 0.0271–1.923, $p = 0.17$) by Fine and Gray assessment, and 0.230 (95% CI: 0.027–1.972, $p = 0.18$) by the Cause-specific hazards model. While there was no significant difference, the HR estimates from both models suggest lower risk of graft failure in HMP-O_2, but these estimates are imprecise given wide CIs that cross one. Within 12 months, 6.3% HMP-O_2 (N = 4) expired a median of 271 days post-transplant from non–

TABLE 2 Baseline liver donor characteristics and liver preservation parameters

	HMP-O_2 N = 63	SCS N = 73	*p*
Donor characteristics			
Donor age, median (IQR)	48 (36, 58)	38 (30, 55)	0.14
Donor sex, female N (%)	23 (36.5)	24 (32.9)	0.66
Donor Race/Ethnicity, N (%)	—	—	0.06
White	44 (69.8)	57 (78.1)	—
Black	7 (11.1)	11 (15.1)	—
Hispanic	12 (19.0)	4 (5.5)	—
Other	0 (0)	1 (1.4)	—
Extended, criteria donor, N (%)	15 (23.8)	21 (28.7)	0.51
DCD	5 (7.9)	10 (13.7)	—
Age > 65	8 (12.7)	9 (12.3)	—
Steatosis > 30%	2 (3.2)	2 (2.7)	—
LDRI, median (IQR)	1.613 (1.397, 1.809)	1.480 (1.225, 1.750)	0.042
Functional WIT (DCD only), median (IQR)	23.0 (21.5, 27.5)	17.5 (12.5, 23.5)	0.060
Donor BMI, median (IQR)	26.9 (23.5, 31.4)	27.4 (23.3, 33.5)	0.75
Donor LFTs, mean (± SD)			
Peak AST, IU/L	288.4 (378.0)	480.4 (840.9)	0.33
Terminal AST, IU/L	111.1 (138.1)	139.3 (436.8)	0.74
Peak ALT, IU/L	213.9 (332.2)	353.4 (665.1)	0.81
Terminal ALT, IU/L	82.0 (159.2)	134.3 (287.1)	0.71
Peak T. Bili, mg/dL	1.18 (0.77)	1.18 (0.87)	0.98
Terminal T. Bili, mg/dL	0.86 (0.75)	0.78 (0.69)	0.77
Peak Alk Phos, IU/L	131.7 (69.4)	109.3 (60.4)	0.029
Terminal Alk Phos, IU/L	96.3 (59.0)	88.1 (53.8)	0.46
Donor liver preservation characteristics			
Cold preservation time (h), median (IQR)	6.4 (5.4, 7.3)	6.8 (1.9, 7.8)	0.25
Preperfusion CIT (h, delayed end-ischemic)	4.1 (2.8, 5.0)	—	—
Initiation of perfusion, N (%)			
Delayed end-ischemic (post-SCS)	36 (57.1)	—	—
Immediate post-procurement	27 (42.8)	—	—
Travel by air	22/27 (81.4)	—	—
Travel by land	4/27 (14.8)	—	—
Donor at LT center	1/27 (3.7)	—	—
HMP-O_2 perfusion parameters		—	—
HMP-O_2 total duration (h), median (IQR)	2.8 (1.8, 3.6)	—	—
< 2, N (%)	19 (30.1)	—	—
2–4, N (%)	33 (52.4)	—	—
> 4, N (%)	11 (17.5)	—	—
HA terminal flow (L/min), median (IQR)	0.17 (0.13, 0.22)	—	—
HA terminal pressures (mm Hg), median (IQR)	30.0 (27.0, 35.0)	—	—
PV terminal flow (L/min), median (IQR)	0.81 (0.74, 0.88)	—	—
PV terminal pressures (mm Hg), median (IQR)	7.0 (6.0, 9.0)	—	—
Perfusate temperature (°C), median (IQR)	6.1 (5.6, 6.9)	—	—
Recipient operative characteristics			
Operative duration (h), median (IQR)	6.0 (3.3, 7.6)	5.8 (3.0, 8.0)	0.99
Intraoperative HD instability, N (%)	6 (9.5)	7 (9.6)	0.99
Blood transfusions, median (IQR)			
RBC, units	6 (3, 8)	6 (1, 11)	0.59
FFP, units	7 (0, 11)	8 (0, 12)	0.56

TABLE 2. (*continued*)

	HMP-O_2 N = 63	SCS N = 73	*p*
Platelet, units	1 (0, 2)	1 (0, 2)	0.56
Autologous blood, mL	458 (0, 1183)	750 (0, 1600)	0.55

Abbreviations: Alk Phos, alkaline phosphatase; CIT, cold ischemia time; Cr, serum creatinine; DBD, donation after brain death; DCD, donation after cardiac death; ECD, extended criteria donor; FFP, fresh frozen plasma; HA, hepatic artery; HD, hemodynamic HMP-O_2, hypothermic oxygenated machine perfusion; LDRI, liver donor risk index; LFT, liver function tests; Plt, platelets; PV, portal vein; RBC, red blood cells; SCS, static cold storage; T Bili, total bilirubin; WIT, warm ischemia time.

liver-related causes (respiratory = 2, cardiac = 1, sepsis = 1). Two (2.7%) patients with SCS expired a median of 72 days following transplant due to graft failure in one and amyloidosis in the second.

Biliary complications were not statistically different between groups (Table 3); however, the frequency of biliary complications in SCS (26.4%, n = 19) was more than double that for HMP-O_2 (12.7%, n = 8, $p = 0.15$). Of these, bile leaks occurred in 1 HMP-O_2 and 2 SCS, who recovered following drainage and/or stenting. A third SCS recipient required operative biliary anastomotic revision due to partial ischemic necrosis of the donor duct. Biliary strictures occurred in 11.1% (N = 7) HMP-O_2. Three (42.9%) occurred <30 days post-LT (median 8 d, IQR: 7.5–9 days) and were potentially technical rather than ischemic. Biliary strictures occurred in 21.9% (n = 16, $p = 0.19$) SCS. Four (25.0%) occurred <30 days post-LT (median 16 days, IQR: 9.8–22.5, $p = 0.18$), while 12 (75%) occurred > 30 days post-LT and were likely ischemic. All biliary strictures in HMP-O_2 were anastomotic; whereas nonanastomotic strictures accounted for 4/16 (25.0%) of strictures in SCS recipients ($p = 0.12$). While not adequately powered for statistical comparison, the prevalence of biliary complications in the SCS ECD subgroup was 38.1% (N = 8), which was 3x greater than in HMP-O_2 ECD recipients (N = 2, 13.3%, $p = 0.14$). Furthermore, all nonanastomotic strictures developing in SCS recipients occurred in the ECD subgroup (N = 4, 19.1%) (Supplemental Table S2, http://links.lww.com/HEP/I166).

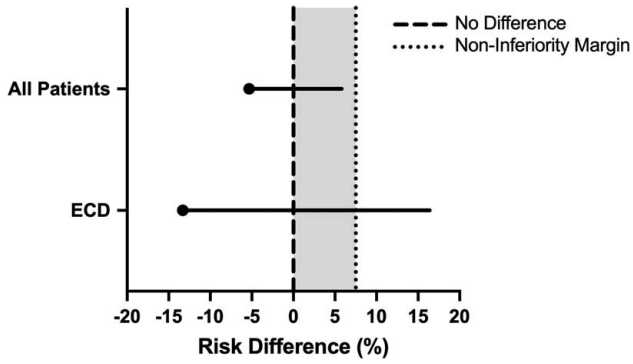

FIGURE 3 Noninferiority analysis of the risk difference for incidence of EAD following liver transplant (primary outcome). Risk difference and the upper limit of the 95% CI are plotted. The dashed line at 0% represents the threshold for no difference, while the dotted line at 7.5% represents the threshold of the noninferiority margin. The gray shaded area denotes the range for results within the noninferiority margin. The upper limit of the 95% CI for all patients falls within the noninferiority margin, establishing noninferiority. The upper limit of the 95% CI for the ECD subgroup exceeds the noninferiority margin. Abbreviation: ECD, extended criteria donors.

Moderate to severe preservation injury was > 3x more common in SCS (13.7%, N = 10) than HMP-O_2 (4.7%, N = 3, Table 3), although the difference did not reach significance ($p = 0.077$). Severe postoperative bleeding was almost 4x more likely in SCS (12.3%, N = 9) compared with HMP-O_2 (3.2%, N = 2), although this difference was not significant ($p = 0.083$, Table 3). Vascular complications were similar between groups with one instance of HAT in HMP-O_2 and one each of HAT and PVT in SCS. Acute kidney injury was also similar between groups [7.9% (N = 5) HMP-O_2, 11.0% (N = 8) SCS, $p = 0.56$]. Median hospital LOS was 9.0 days in both groups ($p = 0.51$), and median intensive care unit LOS was 3.0 days in both groups ($p = 0.58$). In the EAD subgroup analysis, there was a clinically relevant but not statistically significant reduction in total postoperative LOS with a median of 7.0 days with HMP-O_2 versus 16.0 days with SCS ($p = 0.083$).

A total of 295 AEs were documented, with 119 occurring in 43 (68.3%) of HMP-O_2 recipients and 176 occurring in 58 (79.5%) SCS recipients. A median of one AE per patient occurred in HMP-O_2 and 2 AEs per patient in SCS ($p = 0.12$, Figure 5). While this difference was not significant, multiple AEs (3+) were more frequent in SCS (16.4%, N = 12) than HMP-O_2 (3.2%, N = 2, $p = 0.011$). Furthermore, when excluding infectious complications, noninfection-related AEs were more frequent among SCS than HMP-O_2 (Figure 5, $p = 0.044$). A total of 124 AEs were further classified as (SAE), with 46 occurring in 27 (42.9%) HMP-O_2 recipients and 78 occurring in 38 (52.1%) SCS recipients (Figure 5).

While it is not possible to statistically compare AEs, there were some clinically relevant trends noted (Supplemental Table S3, http://links.lww.com/HEP/I167). More than twice the frequency of severe AEs occurred in SCS (27.2%, N = 37) than HMP-O_2 (12.6%, N = 15, Figure 5), and severe noninfectious AEs were almost 3x more common in SCS (19.9%, N = 35) compared with HMP-O_2 (6.7%, N = 8). No cases of severe ischemic/preservation injury were reported in HMP-O_2 (Supplemental Table S3, http://links.lww.com/

TABLE 3 Recipient primary, secondary and exploratory outcomes in per-protocol study population

	HMP-O_2 N = 63	SCS N = 73	*p*
Patient outcomes			
EAD, N (%)	7 (11.1)	12 (16.4)	0.37
$LGrAFT_7$, % risk, median (IQR)[a]			
Study population	3.4 (2.4, 6.5)	4.5 (2.9, 9.4)	0.024
ECD cohort[a]	2.9 (2.4, 4.5)	4.3 (2.9, 9.6)	0.089
PNF, N (%)	0 (0)	3 (4.1)	0.10
Liver-related graft failure, N (%)	1 (1.6)	5 (6.3)	0.14
Re-transplanted, N (%)	1 (1.6)	4 (5.5)	—
Liver-related death, N (%)	0	1 (1.4)	—
One-year mortality, N (%)	4 (6.3)	2 (2.7)	0.99
Graft failure (PNF)	0	1 (1.3)	—
Cardiac	1 (1.6)	0	—
Respiratory	2 (3.2)	0	—
Systemic amyloidosis	0	1 (1.3)	—
Ischemic bowel/sepsis	1 (1.6)	0	—
Moderate to severe ischemic preservation injury[a]	3 (4.7)	10 (13.7)	0.077
Severe postoperative bleeding[a]	2 (3.2)	8 (11.0)	0.083
Biliary complication, N (%)	8 (12.7)	19 (26.4)	0.15
Leak[b]	1 (1.6)	3 (4.1)	—
Anastomotic stricture[c]	7 (11.1)	12 (16.4)	—
Nonanastomotic stricture[d]	0	4 (5.5)	—
Nonanastomotic stricture/ischemic cholangiopathy[c]	0	4 (5.5)	0.12
Vascular complications,[e] N (%)	1 (1.6)	2 (2.8)	0.64
Hepatic artery thrombosis	1 (1.6)	1 (1.4)	0.92
Portal vein thrombosis	0	1 (1.4)	0.35
Acute kidney injury within 7 d, N (%)	6 (9.5)	10 (13.7)	0.45
Acute cellular rejection, N (%)[a]	6 (9.5)	7 (9.6)	0.99
Incisional hernia, N (%)[a]	0	4 (5.48)	0.12
Hospital LOS[f], median (IQR)			
Overall cohort, d	9.0 (6.0, 14.0)	9.0 (6.0, 17.0)	0.51
EAD cohort, d	7.0 (6.0, 13.0)	16.0 (8.3, 22.0)	0.083
ICU LOS[g], d, median (IQR)			
Overall cohort, d	3.0 (2.0, 4.0)	3.0 (2.0, 5.0)	0.58
EAD cohort, d[a]	3.0 (2.0, 4.0)	3.5 (2.0, 7.0)	0.48
Adverse events (AE, per patient), median (IQR)[a]	1 (0, 3)	2 (1, 3.5)	0.12
Noninfection-related AE (per patient), median (IQR)[a]	0 (0, 2)	1 (0, 2.5)	0.044
Multiple adverse events (3+), N (%)[a]	2 (3.2)	12 (16.4)	0.011
Serious adverse event (per patient), median (IQR)[a]	0 (0, 1)	0 (0, 2)	0.23
Post-reperfusion labs			
Peak lactate, mmol/L, mean (±SD)	3.93 (3.3)	3.62 (2.55)	0.67
Peak AST, IU/L, mean (±SD)	1789.9 (1719.2)	2037 (2835.7)	0.53
Peak ALT, IU/L, mean (±SD)	767.5 (620.7)	800.2 (832.7)	0.79
Peak Cr, mg/dL, mean (±SD)	2.2 (1.4)	2.2 (1.3)	0.89
Peak INR, mean (±SD)	1.9 (0.7)	1.9 (0.6)	0.92

[a]Indicates *post hoc* analysis variable.
[b]Defined as CT or drainage catheter evidence of bile leak in absence of hepatic artery thrombosis.
[c]Defined as anastomotic bile duct narrowing with ERCP evidence of biliary ductal dilation requiring endoscopic or surgical intervention.
[d]Defined as nonanastomotic/intrahepatic narrowing with ERCP evidence of biliary ductal dilation or biliary casts.
[e]Defined as PVT and/or hepatic artery thrombosis.
[f]Defined as time from transplant to hospital discharge.
[g]Defined as time from transplant to ICU transfer order.
Abbreviations: AEs, adverse events; Cr, creatinine; EAD, early allograft dysfunction; ECD, extended criteria donor; HMP-O_2, hypothermic oxygenated machine perfusion; $LGrAFT_7$, liver graft assessment following transplantation; LOS, length of stay; PNF, primary nonfunction; SCS, static cold storage; T Bili, total bilirubin.

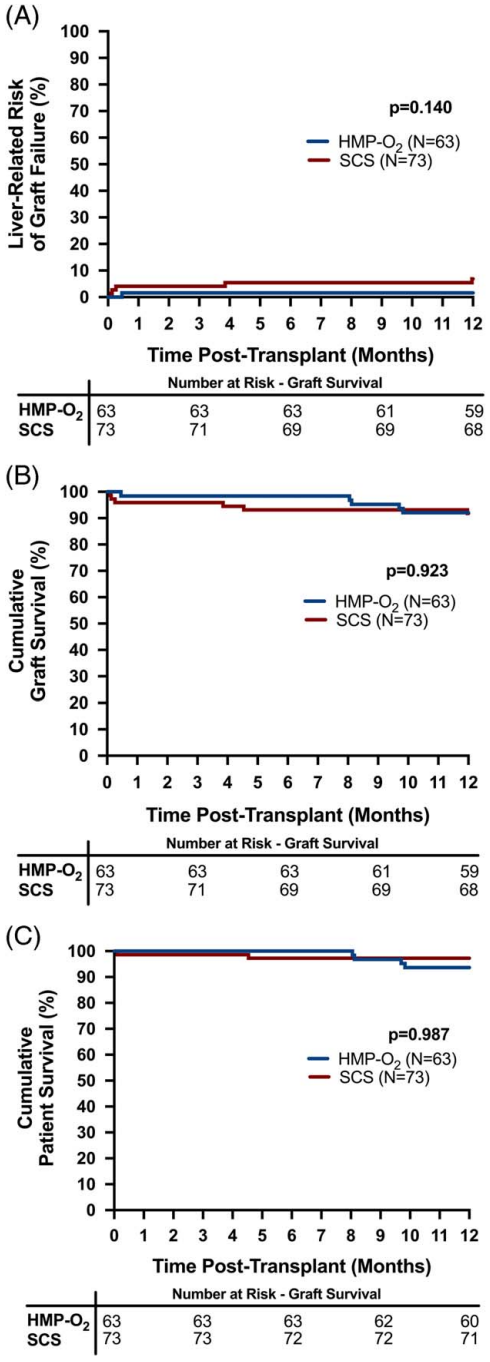

FIGURE 4 Graft and patient outcomes following liver preservation with HMP-O_2 and SCS in the first year following liver transplant. (A) The cumulative risk of graft failure demonstrates a decreased incidence following liver transplant with HMP-O_2 (blue line) compared with SCS (red line), but difference was not statistically significant ($p = 0.140$). (B) Cumulative graft survival and (C) cumulative patient survival are not significantly different within the first year following liver transplant. Abbreviations: HMP-O_2, hypothermic oxygenated machine perfusion; SCS, static cold storage.

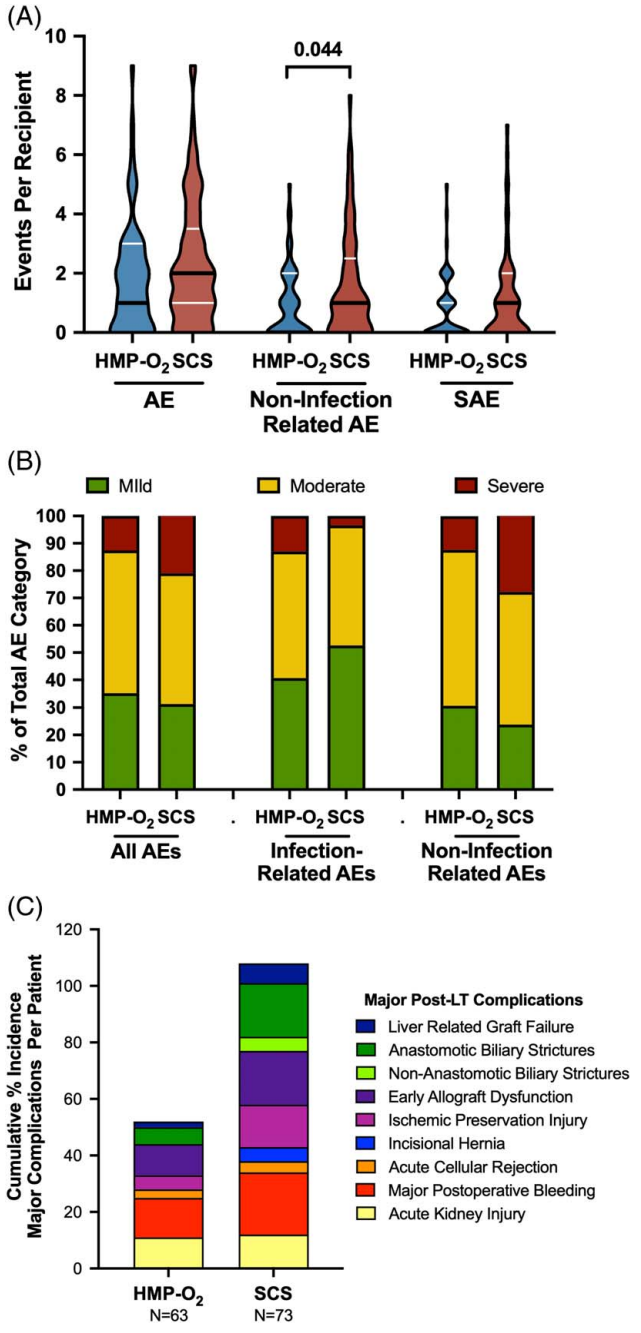

FIGURE 5 Adverse events in recipients of livers preserved by HMP-O_2 or SCS. (A) Violin plot demonstrating the distribution of AEs and SAEs occurring in each patient cohort. Thick black line represents the median value, and thin white line represents the quartiles. (B) The proportion of AEs classified as mild (green), moderate (yellow), and severe (red) for all AEs, infection-related AEs, and noninfection-related AEs. Proportion is related to the number of AEs for each subclassification per cohort. (C) The cumulative (additive) %incidence of major noninfection-related post-transplant complications in patients for each cohort is shown. Each bar subdivision represents the proportion of patients in the cohort develop the complication specified by the stacked colored bars. Abbreviations: AEs, adverse events; HMP-O_2, hypothermic oxygenated machine perfusion; LT, liver transplant; SAE, serious adverse event; SCS, static cold storage.

HEP/I167). Moderate to severe infection-related AEs were slightly more frequent in HMP-O_2 than in SCS. On further stratification, infection-related AEs in HMP-O_2 were more likely to occur > 30 days post-transplant.

Systemic viral infections (eg, Cytomegalovirus (CMV)) or nonincision-related skin and soft tissue infections were more prevalent in HMP-O_2, and these are unlikely related to perioperative events. The cumulative (additive) incidence of noninfection-related major post-transplant complications per patient is shown in Figure 5.

DISCUSSION

The results of the PILOT RCT demonstrate the safety and noninferior efficacy of a portable technique of oxygenated HMP using the LLT in clinical LT. Nine transplant centers in a variety of locations and practice types successfully integrated this technique into clinical practice. Ease of use, portability, and the inherent cold storage backup afforded by this technique's design are important factors in its safety and flexibility and may facilitate widespread adoption.

This was an FDA pivotal trial with a primary endpoint based on noninferiority of EAD between HMP-O_2 and SCS by strict definition.[21] Results demonstrate noninferiority of HMP-O_2 compared with SCS, with a significant decrease in noninfection-related AEs and multiple AEs in HMP-O_2 recipients. Noninfection-related AEs include the occurrence of graft failure due to PNF and ischemic cholangiopathy, both of which only occurred in SCS recipients. Furthermore, while not statistically significant, there was a clinically notable decrease in severe postoperative bleeding and biliary complications in HMP-O_2 recipients, as well as a decrease in overall hospital LOS in HMP-O_2 recipients developing EAD. Of note, trial enrollment allowed for the inclusion of both standard donors and ECDs. Only a quarter of our cohort received ECD livers. The benefits of HMP-O_2 may be even more pronounced in a purely ECD cohort, as has been shown with other devices and in other trials.[8]

Power calculations employed to determine study population size were based on noninferiority study design and not designed to detect differences in overall EAD rates. Despite this, analysis of EAD approached the threshold of superiority for HMP-O_2 over conventional SCS. While EAD is a commonly used metric of graft function, its utility as a primary outcome measure has recently been re-evaluated due to its binary nature,[15,29,30] and it has become outdated. More robust graft dysfunction prediction modeling is employed by many groups.[22] Most HMP-O_2 EAD cases were triggered by 1 or 2 elevated early postoperative AST values. AST can fluctuate with graft weight or recipient volume status, limiting its utility. It was not uncommon to have HMP-O_2 subjects meet EAD criteria but have a total hospital LOS < 7 days. In the subgroup analysis of subjects with EAD, HMP-O_2 experienced shorter hospital LOS and fewer complications, although this difference was not significant.

L-GrAFT$_7$ was not included in the original study design because its validation occurred concurrently with the study onset. Given its superiority, it was included in *post hoc* analysis to increase sensitivity of graft function assessment.[22,23] L-GrAFT$_7$ score provides continuous modeling of early allograft function by predicting risk of graft failure at 3 months based on longitudinal laboratory variables over the first 7 days post-LT. L-GrAFT$_7$ scores demonstrated a significantly reduced risk of graft failure in patients receiving HMP-O_2 livers compared to SCS. In subgroup analysis of ECD livers, this finding remained, although it was not significant. Although it also did not reach significance, analysis of graft loss secondary to liver failure mirrored these results, with increased graft failure following SCS.

From a technical standpoint, our perfusion protocol is a dual flow (HA/PV) technique that we have used since early prototype work,[5,10] similar to what is described as Dual-Hypothermic Oxygenated machine PErfusion (D-HOPE).[8] Despite the similarities in vascular perfusion, there are obvious differences in equipment, flow rates, perfusate composition, and oxygenation technique, which may affect the relative benefits achieved with HMP-O_2. Several European RCTs have demonstrated the benefits of HMP-O_2 using D-HOPE. These include decreased severe liver-related complications such as PNF and biliary complications.[15] In contrast to the D-HOPE device, the LLT is portable, expanding the potential for immediate placement of transported liver on the pump. RCT trials with end-ischemic D-HOPE have already demonstrated several potential benefits for HMP-O_2 in DCD and ECD recipients, including decreased EAD,[8,16,19] nonanastomotic biliary strictures[8] shorter intensive care unit, and hospital stays,[16] 90-day complications,[16,19] and improved 1-year graft.[19] While our study was not powered to detect these differences, HMP-O_2 with the LLT demonstrated similar findings, including a significantly decreased risk of graft failure after HMP-O_2 as measured by LGrAFT$_7$ along with a significant decrease in noninfection-related AEs. Despite the protocol differences, our hypothesis is that any dynamic hypothermic oxygenated perfusion technique adds benefit. With anticipated adoption of HMP-O_2, building clinical experience will clarify optimal parameters for perfusion and allow tailoring of protocols to center needs.

Perhaps the most exciting benefit of HMP-O_2 is the reduction in biliary complications,[8] especially the difficult-to-manage ischemic type intrahepatic strictures associated with DCD livers. While our ECD cohort was small with few DCDs, only 2 HMP-O_2 ECD recipients developed biliary complications compared with 38% of SCS recipients, and no HMP-O_2 recipients developed nonanastomotic strictures. In contrast, 4 occurred in SCS, including 2 patients requiring retransplant, all of which were ECD recipients. While this may be an anecdotal finding, we look forward to gaining further multicenter experience with the LLT, especially in ECD livers.

One potential benefit of the LLT is its transportability. In the present study, almost half of livers were immediately placed on the pump at the donor hospital. We expect an increase in immediate pump placement as centers gain experience in traveling with the pump. The device provides flexibility for end-ischemic perfusion in cases where the organ is procured by another center. Future implementation of immediate perfusion at the organ procurement organization (OPO) level could potentially increase recovery of livers declined in the OR, DCD livers, or livers without an intended recipient at procurement. Whether immediate versus end-ischemic HMP-O_2 best optimizes outcomes requires additional study, but it may especially add benefit in ECD and DCD donors.

In this study, we saw several models of utilization: some were center-based, while others were OPO-driven. We believe there are many different potential applications of HMP-O_2 in LT, and each center or OPO will determine the best model and logistics for the implementation of this technique. OPOs are key stakeholders in the process and have historically shown substantial interest in providing these services. Business models, costs, and reimbursement, as well as center "return on investment" are beyond the scope of this discussion, but these are frequent topics of robust discussion among transplant professionals.

As we enter a period of rapid adoption of multiple perfusion techniques at different temperatures, we anticipate that the LLT device with Vasosol will offer many attractive advantages, including ease of use, cost, safety features, and complete portability. The potential benefits to using the device include improved clinical outcomes with reduced complications, optimization of center logistics including performance of semielective cases, and expanded and more aggressive use of ECD/DCD livers without compromising results. We believe that the adoption of HMP-O_2 will allow program leadership more flexibility and confidence in program strategy, and it will allow the expansion of transplant volume with excellent outcomes.

There are several limitations to our study. The study randomization protocol resulted in a relative imbalance of interventions to achieve study-wide rather than center-balanced enrollment. The lack of center-level randomization resulted in one center having almost double the ratio of control- to treatment-arm (SCS = 14, HMP-O_2 = 7), while another center had the inverse (SCS = 15, HMP-O_2 = 23). This introduces a bias that may have implications for extrapolating results. While the donor and recipient populations were well-matched, center-specific variability, such as protocol approach and transplant practices, was an unavoidable confounder we acknowledge. This study was designed as an FDA pivotal trial to evaluate noninferiority to SCS to obtain 510(k) device clearance rather than to detect superiority of HMP-O_2. We were primarily reliant on standard criteria donors, which have excellent survival outcomes. Due to this, the cost and time necessary to adequately power a superiority study would have been greatly increased. The protocol-defined intent-to-treat analysis required modification due to early major protocol violations and preperfusion device–unrelated reversion to SCS and is a potential source of bias. This mITT was used for device safety assessment while we focused on the per-protocol assessment for device efficacy. In addition, we did not apply procedures for hierarchical testing or multiple testing correction in the original analysis; therefore, the secondary end points can only be interpreted as exploratory and hypothesis-generating rather than confirmatory. While secondary complications such as nonischemic biliary strictures and PNF were decreased in HMP-O_2, they were not statistically significant. The study sample size was powered for noninferiority of the primary outcome of EAD. Additional accrual is necessary to determine the significance of secondary outcomes. An expanded patient population, including additional ECD recipients, is critical to discerning the ultimate benefit of HMP-O_2. Finally, the minimum CIT requirement for study enrollment was relatively short; therefore, perfusion times varied from <1 hour to >6 hours. In retrospect, the inclusion of a minimum perfusion time in the study protocol may have been advisable. We anticipate that trial continued access and subsequent adoption into clinical practice will demonstrate extended CIT to facilitate logistics and "daytime" transplant case, as the feasibility of extended machine perfusion has already been reported by other groups.[31,32]

In conclusion, the results of the PILOT RCT demonstrate the safety and noninferior efficacy of the LifePort Liver Transporter and Vasosol for Hypothermic Oxygenated Machine Preservation of donor livers in a variety of settings and transplant programs in the United States.

AUTHOR CONTRIBUTIONS

All listed authors contributed greatly to this study and fulfilled the stated guidelines for authorship, as described by the published criteria for authorship by the ICMJE. Each author participated sufficiently in the work to take public responsibility for appropriate portions of the content. Below is the detailed account of each author's contribution: Guergana G. Panayotova: substantial contributions to design of analysis; data acquisition, analysis, interpretation, and verification; drafting of the article; and final approval of the version to be published. Keri E. Lunsford: study site investigator, substantial contributions to design of analysis; data acquisition, analysis, interpretation, and verification; drafting and revision of the article; and final approval

of the version to be published. R. Cutler Quillin III: study site investigator, substantial contributions acquisition of data; critical revision of the manuscript for intellectual content; and final approval of manuscript. Abbas Rana: substantial contributions to data analysis and interpretation, critical review of underlying reported data, critical revision of the manuscript, and final approval of manuscript. Vatche G. Agopian and Daniela Markovic: substantial contributions to the interpretation of data, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. Grace S. Lee-Riddle: substantial contributions to interpretation of data and critical revision of the manuscript for important intellectual content, and final approval of the version to be published. Flavio Paterno: study site investigator; substantial contributions to data acquisition and critical revision of the manuscript; and final approval of the version to be published. Adam D. Griesemer, Diane Alonso, Juan P. Rocca, Daniel Borja-Cacho, Roberto Hernandez-Alejandro, John J. Fung, Shawn J. Pelletier, Shimul A. Shah: Study site lead investigator; substantial contributions to acquisition of data; critical revision of the manuscript; and final approval of the version to be published. Arpit Amin: study site investigator; substantial contributions to acquisition of data; critical revision of the manuscript; and final approval of the version to be published. James V. Guarrera: substantial contributions to conception and design of the study; lead investigator on the clinical trial; acquisition, analysis, and interpretation of data for the work; verifying data analysis and critical review of underlying reported data; drafting and revision of the article; critical revision of the manuscript for important intellectual content, and final approval of the version to be published.

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CONFLICTS OF INTEREST

Guergana G. Panayotova received travel grants from Organ Recovery Systems. Keri E. Lunsford consults for GATT Technologies. She owns stock in Henry Schein, Incyte, Intellia Therapeutics, Johnson & Johnson, ROM Tech, and Tandem Diabetes. R. Cutler Quillin, III consults and received travel grants for Ethicon. Grace S. Lee-Riddle consults for EBSCO-Dynamed. Daniel Borja-Cacho received travel grants from Organ Recovery Systems and Xvivo Perfusion. Shimul A. Shah consults and advises Genentech. He received grants from CareDx and Organ Recovery Systems. James V. Guarrera consults and received travel grants from GATT Technologies and Organ Recovery Systems. The remaining authors have no conflicts to report.

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