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Normothermic Machine Perfusion Reduces Transfusion Requirements Even After Static Cold Storage: A 1 y Retrospective Single-center Analysis

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Background. Normothermic machine perfusion (NMP) of liver grafts has been shown to reduce intraoperative catecholamine consumption and the need for allogenic blood products after reperfusion compared with organs undergoing classical static cold storage (SCS). This study aimed to investigate the effects of an NMP phase after SCS (NMP after SCS) of liver grafts in terms of postreperfusion hemodynamics and transfusion requirements. **Methods.** Eighteen recipients of NMP after SCS grafts were matched according to recipient age, donor age, and model for end-stage liver disease score in a 1:2 ratio with recipients of an SCS graft. Postreperfusion hemodynamics and the need for catecholamines, blood products, and clotting factors were compared. **Results.** After reperfusion of the organ, patients in the NMP after SCS group showed significantly reduced transfusion requirements for packed red blood cells and platelet concentrates compared with patients of the SCS group ($P < 0.001$ and $P = 0.018$, respectively). In addition, patients in the NMP after SCS group received less fibrinogen concentrate (NMP after SCS group 0 [0–1.5] g versus SCS group 2 [0–4] g; $P = 0.0163$). No differences in postreperfusion hemodynamics could be detected between groups. **Conclusions.** This retrospective analysis shows that NMP reduces postreperfusion requirements of red blood cells, platelet concentrates, and fibrinogen concentrate even if installed after a phase of organ SCS, because it may be practiced on most centers where NMP is available.

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O rthotopic liver transplantation (OLT) is the accepted standard of care for irreversible acute or chronic liver failure. Nevertheless, OLT remains a high-risk procedure that may be associated with distinct perioperative blood

loss, hemodynamic instability, and perioperative renal failure with an important impact on postoperative morbidity and mortality.[1-4]

Normothermic machine perfusion (NMP) has evolved as a new strategy to better preserve high-risk grafts from detrimental effects of ischemia compared with static cold storage (SCS), especially in high-risk organs.[5-7] Recently, it has been shown that NMP reduces posttransplant early allograft dysfunction and ischemic biliary complications.[8] Apart from that, NMP seems to have beneficial effects on the so-called extended donor criteria organs in case of difficult logistics (eg, parallel transplantations) and in highly complex recipients.[6] The opportunity of functional organ assessment during storage increases the probability of transplantation and thus counteracts organ shortage.[5]

Recent studies have shown that NMP also seems to impact recipient's intraoperative hemodynamics, coagulation function, and the amount of required blood transfusions immediately after reperfusion of the graft.[9,10] In these studies, however, the cold ischemic time (CIT) of the explanted organs was very short because NMP was started immediately after the cold perfusion of the donor. At the Medical University of Innsbruck, NMP is started after the graft arrives from a hospital in the Eurotransplant area, which implies a cold storage period of several hours. Until now it is not clear whether the beneficial effects of NMP are present after several hours of SCS. We therefore aimed to investigate the effects of NMP

after SCS on recipient hemodynamics, coagulation function, and blood loss during the immediate postreperfusion phase compared with a matched group of patients who received a liver graft after SCS only.

MATERIALS AND METHODS

This retrospective single-center study was approved by the local ethics committee (EK No. 1022/2021; March 18, 2021). All patients who underwent liver transplantation after NMP between February 2018 and June 2019 were identified from our institutional OLT database. Patients younger than 18 y and patients with a history of liver transplantation (retransplantation) were excluded. Once liver transplant recipients after NMP after SCS were identified, a matched pair control group (1:2) was created. The control group consisted of OLT recipients after SCS between 2015 and 2019. The control group was matched according to recipient age (±10 y), donor age (±5 y), and model for end-stage liver disease score (±2). Patients without matching partners, according to these criteria, were excluded from analysis. Donor characteristics were obtained from "Eurotransplant International Foundation," the central coordination institution for organ donation and transplantation in central Europe.

Organ Preservation

According to local standard operating procedure, SCS was performed by perfusion of the retrieved organ with "histidine-tryptophan-ketoglutarate" solution (HTK) and then storage on ice until implantation. Grafts not procured at our center were perfused according to local guidelines with either HTK or the "University of Wisconsin" solution and then stored on ice for transportation. After arrival at our hospital, NMP grafts were surgically prepared for NMP and connected to the Metra liver perfusion device. The liver remained in the perfusion device until immediately before implantation, and it was then flushed with HTK and implanted according to local standard procedure.

Intraoperative Parameters

The primary objective was to assess whether the 2 study groups differed in relation to postreperfusion hemodynamics and the perioperative need for transfusion of allogenic blood products and coagulation factors. Anesthesiologists followed local standard procedures in which mean arterial pressure >65 mmHg is targeted throughout transplantation, and clotting factor substitution is indicated by using rotational thromboelastometry. To allow for more precise temporal analysis, the intraoperative course was divided into 3 phases: hepatectomy (time from the beginning of surgery to vascular clamping of the pathological liver), anhepatic phase (time from the vascular clamping of the pathological liver to reperfusion of the liver graft), and post reperfusion phase (time from reperfusion to the end of surgery). Based on previous work, a 1-min drop in mean arterial pressure of >30% during the first 5 min after reperfusion compared with the last 10 min before reperfusion was defined as a postreperfusion syndrome (PRS).[11] As catecholamines were administered to treat hypotension, we calculated catecholamine requirements as a surrogate parameter using our automated digital anesthesia recordings at 1-min time intervals. Moreover,

transfusion of blood products (packed red blood cells [RBCs], platelet concentrates [PCs], and fresh frozen plasma [FFP]) and coagulation factor concentrates (fibrinogen, prothrombin complex concentrates [PCC; factors II, X, VII, and IX]) were extracted from the anesthesia protocol and compared for each phase. In addition, duration of the phases and acid/base status (pH, base excess, and lactate) were assessed for both groups. Recipient hemoglobin levels and coagulation parameters (prothrombin time, partial thromboplastin time, fibrinogen concentration, and antithrombin) were recorded and compared between groups before the start of transplantation and on admission to the intensive care unit (ICU) immediately after surgery.

Postoperative Parameters

Liver function parameters (aspartate aminotransferase [AST], alanine aminotransferase, gamma-glutamyltransferase, cholinesterase, alkaline phosphatase, and bilirubin) were documented for the first 7 postoperative days. A comparison was also made of the incidence and duration of renal replacement therapy, the rate of postoperative endoscopic retrograde cholangiopancreatography (ERCP), and the length of intensive care stay and hospital stay.

Statistics

Descriptive statistics (medians with 25th–75th percentile, frequencies, and percentages for categorical variables) was calculated for the study variables and demographic data. A Wilcoxon rank-sum test was used to analyze continuous variables and the Fisher exact test was used to analyze categorical variables. A P value of <0.05 was considered as a statistically significant difference.

RESULTS

A total of 26 liver grafts were transplanted after NMP after SCS from February 2018 to June 2019. Five recipients had to be excluded because of retransplantation; 1 patient had to be excluded because of missing data. Because no SCS transplantation met the matching criteria (±5 y donor age, ±10 y recipient age, ±2 model for end-stage liver disease score) in the defined study period, 2 additional recipients of a liver graft after NMP after SCS had to be excluded. The final data analysis included data from 18 NMP after SCS patients and 36 matched SCS recipients.

General Parameters

Patient demographics, CIT, and warm ischemic time are presented in Table 1. With the exception of the higher incidence of donation after circulatory death donors in the NMP after SCS group, the groups are well matched. All transplantations were performed by the cava replacement technique without the use of a portocaval shunt. CIT between the 2 groups did not differ; NMP after SCS grafts were perfused for 12 h and 37 min (565–1117 min) before implantation. Warm ischemic time between removal from ice and reperfusion in the recipient (SCS group) or termination of NMP and reperfusion of the graft in the recipient (NMP after SCS group) was significantly longer in the NMP after SCS group (NMP after SCS group 50 [46–52.5] min compared with the SCS group 41 [38.5–48.5] min; P = 0.0236).

TABLE 1.

Demographic and preservation details

	NMP after SCS (N = 18)	SCS (N = 36)	Estimate with 95% CI	*P*
Donor characteristics				
Age donor, y	64.5 (55.75–68)	64 (54.5–69)	0 (–5 to 7)	0.92
Sex of donor (female)	9 (51.9%)	19 (52.8%)	1.12 (0.31 to 4.03)	1
Donor type (DCD)	4 (22.22%)	1 (2.78%)	10 (1.03 to 97.50)	**0.048**
Mild steatosis	7 (38.89%)	4 (11.11%)	5.09 (1.16 to 17.33)	**0.03**
Moderate steatosis	2 (11.11%)	4 (11.11%)	1 (0.18 to 4.69)	1
Donor ICU stay, d	4 (3–7.25)	4 (1.25–6.75)	1 (–1 to 3)	0.314
Recipient characteristics				
Age recipient, y	65 (56.5–67)	63 (56.5–66)	1 (–2 to 5)	0.485
Sex of recipient (female)	1 (5.6%)	10 (27.8%)	6.36. (0.78 to 299.7)	0.077
Cause of liver failure				
Alcoholic	6 (33.33%)	12 (33.33%)	1 (0.29 to 3.56)	1
Hepatitis B	1 (5.56%)	1 (2.78%)	2.06 (0.12 to 34.95)	1
Hepatitis C	1 (5.56%)	11 (30.56%)	0.13 (0.02 to 1.13)	**0.044**
Hepatocellular carcinoma	5 (27.78%)	8 (22.22%)	1.35 (0.39 to 4.85)	0.74
Nonalcoholic steatohepatitis	2 (11.11%)	3 (8.33%)	1.38 (0.23 to 7.24)	1
Primary sclerosis cholangitis	0 (0%)	1 (2.78%)		0.107
Alpha 1 antitrypsin	2 (11.11%)	0 (0%)		0.107
Budd Chiari syndrome	1 (5.56%)	1 (2.78%)	2.06 (0.10 to 40)	1
Portal hypertension	14 (77.8%)	31 (86.1%)	1.77 (0.48 to 7.5)	0.461
Previous upper abdominal surgery	4 (22.2%)	3 (8.3%)	3.14 (0.75 to 13.45)	0.205
Preservation characteristics				
Cold ischemic time, min	409 (356.25–470)	446.5 (343.75–506.5)	–32.24 (–100 to 51)	0.452
Warm ischemic time, min	50 (46–52.5)	41 (38.5–48.5)	7 (1 to 11)	**0.024**
NMP time, min	757 (545–1116.5)	–		

P < 0.05 are significant (presented in bold).

CI, confidence interval; DCD, donation after circulatory death; ICU, intensive care unit; NMP, normothermic machine perfusion; SCS, static cold storage.

Intraoperative Parameters

Hemodynamic parameters, such as mean arterial pressure, central venous pressure, and mean pulmonary arterial pressure, did not differ between groups at any time point. The need for noradrenaline administration did not differ between groups after reperfusion (NMP after SCS group 0.02 [0.01–0.04] µg/kg/min versus SCS group 0.01 [0–0.04] µg/kg/min; *P* = 0.6268). In the SCS group, 5 patients (13.9%) developed a PRS, compared with 1 patient (5.6%) in the NMP after SCS group. However, this difference was not significant (*P* = 0.651).

At baseline, there was no difference in hemoglobin concentration, platelet count, and levels of plasmatic coagulation parameters between groups. Neither during hepatectomy nor in the anhepatic phase, the number of transfused RBC, PCs, and FFP differ between groups. After reperfusion of the graft, patients receiving a SCS liver graft required more units of RBCs (NMP after SCS group 1 [0–2] versus SCS group 3 [2–4]; *P* = 0.0001) and PCs (NMP after SCS group 1 [0–1] versus SCS group 1 [1–2]; *P* = 0.0181). The amount of FFP administered did not differ between groups. The use of cell salvage was documented in all NMP after SCS recipients and in 34 SCS recipients. There were no differences between groups in the amount of cell salvage concentrate administered (NMP after SCS group: 1008 [487.5–1450] mL versus SCS group 1100 [589–1434] mL; *P* = 0.905). On admission to the ICU, no difference in hemoglobin concentration or platelet count was seen between the 2 groups (Table 2).

Substitution of fibrinogen concentrate was similar between groups before reperfusion of the liver graft. However, after reperfusion, patients in the SCS group needed more fibrinogen concentrate compared with patients in the NMP after SCS group (NMP after SCS group 0 [0–1.5] g versus SCS group 2 [0–4] g; *P* = 0.0163). At admission to the ICU, fibrinogen levels did not differ between the groups. Both groups received the same amount of PCC during surgery.

The total duration of surgery was not different between groups. However, the time from skin incision to reperfusion of the liver graft was significantly longer in patients of the NMP after SCS group compared with patients of the SCS group (NMP after SCS group 223 [185.75–252.5] min versus SCS group 183 [133–216.5] min; *P* = 0.0248). Both acid/base status parameters (pH and base excess) and lactate were comparable between groups throughout the course of surgery.

Postoperative Parameters

From postoperative day 4 onward, patients receiving an NMP after SCS liver graft had significantly lower AST values; all other liver function parameters showed no difference between groups. In the SCS group, 12 recipients (66.7%) required ERCP; in contrast, in the NMP after SCS group 13 patients (36.1%) required ERCP (*P* = 0.038). Both the incidence of dialysis and the length of time on dialysis were comparable between the 2 groups. The median length of stay in the ICU was 4.5 d in both groups (NMP after SCS group 4.5 [3.25–8.25] d versus SCS group 4.5

TABLE 2.

Coagulation parameters and transfusion requirements

	NMP after SCS (N = 18)	SCS (N = 36)	Estimate with 95% CI	P
Baseline				
Hb, g/L	10.9 (9.67–13.03)	11.8 (10.6–13)	−0.6 (−1.7 to 0.8)	0.403
Platelets, g/L	110.5 (73–152.25)	95 (62.75–126)	17 (−12 to 45)	0.271
Fibrinogen, mg/dL	253 (229.5–303)	222 (188.25–368.5)	28 (−38 to 74)	0.335
Prothrombin time, %	64 (52.25–75)	61 (50.75–72)	3 (−8 to 13)	0.544
Partial thromboplastin time, s	39.5 (35–42)	40 (35–42)	0 (−4 to 3)	0.890
Antithrombin, %	57 (50–66)	46 (40–59)	10 (0 to 19)	0.053
Hepatectomy				
RBC	3 (1.25–5)	2 (1–4)	1 (−1 to 2)	0.25
PC	0 (0–0)	0 (0–0)	0 (0 to 0)	0.562
FFP	14.5 (10–17)	11 (8.75–15)	2 (−2 to 5)	0.325
Anhepatic phase				
RBC	1.5 (1–3.75)	2 (1–3.25)	−1 (−1 to 1)	0.344
PC	0 (0–0)	0 (0–0)	0 (0 to 0)	0.151
FFP	8 (5–8.75)	6 (5–9)	0 (−1 to 2)	0.739
Postreperfusion phase				
RBC	1 (0–2)	3 (2–4)	−2 (−3 to −1)	**0.0001**
PC	1 (0–1)	1 (1–2)	−1 (−1 to 0)	**0.018**
FFP	8.5 (5.25–11)	9 (7–10)	0 (−2 to 2)	0.883
ICU admission				
Hb, g/L	10.05 (8.53–10.9)	9.9 (9.17–10.3)	0 (−0.8 to 0.8)	0.971
Platelets, g/L	65.5 (47.75–86.75)	59.5 (50.5–77)	2 (−13 to 19)	0.776
Fibrinogen, mg/dL	219 (208.25–248)	219 (197–235.25)	5 (−18 to 29)	0.693
Prothrombin time, %	64 (59.75–70.75)	58.5 (51–66)	6 (0 to 12)	0.054
Partial thromboplastin time, s	38.5 (35.25–40.75)	43 (39.5–51.25)	−6 (−10 to −2)	**0.002**
Antithrombin, %	68.5 (57.5–73)	62.5 (55.5–70.5)	4 (−3 to 12)	0.255

P < 0.05 are significant (presented in bold).

CI, confidence interval; FFP, fresh frozen plasma; Hb, hemoglobin; ICU, intensive care unit; NMP, normothermic machine perfusion; PC, platelet concentrate; RBC, packed red blood cell; SCS, static cold storage.

[3–8.25] d; *P* = 0.7458). Recipients of an NMP after an SCS liver graft were discharged from the hospital after a median of 18.5 d (12.25–22.75) and recipients of an SCS liver graft after 18 d (13–27.5; *P* = 0.74). One patient in the SCS group died of sepsis before hospital discharge.

DISCUSSION

The main finding of this retrospective observational study was that NMP implemented after a mean time of 6.8 h of SCS, has beneficial effects in reducing transfusion requirements for RBCs and PCs after reperfusion of the graft. Additionally, the need for transfusion of fibrinogen concentrate was reduced compared with patients who received a liver graft after SCS alone. Although studies have already described reduced transfusion requirements during liver transplantation after NMP, the surgical logistics of NMP differs significantly in the present study; Dixon et al[12] implemented NMP as fast as possible at the site of explantation, resulting in a short SCS time in the NMP after SCS group (2.1 [1.9–2.6] h). In the second publication showing a reduced need for blood products after NMP, NMP was also started immediately after explantation, resulting in an even shorter SCS time (1.5 [1.2–2.0] h), which also differed significantly from the cold storage duration of the SCS group.[9] The primary objective of our study was to investigate whether an NMP phase implemented after standard cold storage in a back-to-base approach can still promote the positive effects, which have been reported before.

In the present work, each donor organ underwent standard SCS during transportation from the donor hospital to our center, as NMP was not established until the graft arrived at our transplantation center, resulting in a markedly longer SCS time (6.8 [5.9–7.8] h) compared with previously mentioned studies, which did not differ from the SCS group.[9,12] Although the safe applicability of this strategy has already been demonstrated in principle, it was unclear whether the reported advantages of saving blood products could be transferred to this technique.[13]

Another point to be underlined that distinguishes this study from previous studies is the administration of FFP. In the present study, FFP was used for intravascular volume replacement and coagulation factors, such as fibrinogen and PCCs, were administered according to rotational thromboelastometry, resulting in the same amount of FFP in both groups. In previous studies, significantly more FFP was administered to patients in the SCS group than in the NMP group, which makes it very likely that dilution led to lower values of concentration-based parameters such as hemoglobin and platelet count, increasing the number of transfused RBCs and PCs.[12]

Several factors could be responsible for the observed notable savings in RBCs, PCs, and fibrinogen concentrate. First, it is known that the duration of CIT is causally related to the incidence of postoperative complications.[14,15] Therefore, it is of prime importance to keep the hepatectomy time and anhepatic phase as short as possible, thereby focusing on rapid hepatectomy. Our data revealed that the time from the start

of surgery to reperfusion of the graft was significantly longer in the NMP after SCS group compared with the SCS group; this finding could indicate that more time was spent on surgical preparation before hepatectomy. During the hepatectomy phase, significant blood loss can occur; precise and often time-consuming surgical preparation is therefore mandatory. Although logistically well-planned liver transplantation should not be accompanied by time pressure, NMP may allow surgeons to spend more time on precise and extensive surgical hemostasis, which could translate into reduced blood loss. This aspect represents a major difference to organs stored on ice, where every additional surgical minute before hepatectomy increases CIT, which is known to negatively influence graft function outside a certain time frame.[16]

A second fact that may reduce blood loss after NMP after SCS could be the different flushing volumes used. Flushing of liver grafts immediately before reperfusion occurs differently in NMP after SCS compared with SCS grafts. In our transplant center, the organ is flushed with patient blood in a standardized way by releasing the clamp of the freshly anastomosed portal vein and collecting the blood in the inferior vena cava to prevent vasoactive substances from entering the systematic circulation.[17] The collected blood is eventually retransfused via a cell saver system. Inevitably, this procedure results in a status of transient hypovolemia, which can lead to acute hemodynamic instability of the recipient. NMP of the graft, however, seems to reduce inflammation and the accumulation of vasoactive substances in the organ.[17] Although flush volumes are not documented at our center because of the difficulty of accurately measuring the volume in the cell saver reservoir, the authors have the impression that lower flush volumes are accepted for NMP grafts than grafts after SCS.

Furthermore, it has already been shown that NMP significantly reduces ischemia/reperfusion injury compared with SCS.[18] Among other mechanisms, ischemia/reperfusion injury is responsible for the destruction of the endothelial glycocalyx, a key player for vascular integrity and organ function. Disruption of the endothelial glycocalyx leads to numerous pathophysiological processes, including cell damage, tissue injury, sympathoadrenal activation, activation of hemostasis/thrombosis, or bleeding and inflammation.[19] Studies have shown that the integrity of the glycocalyx is of prime importance for physiological organ function, also during liver transplantation.[20,21] Although a previous study has demonstrated glycocalyx damage during machine perfusion of the kidney, possibly induced by altered perfusate composition and laminar flow, it remains unclear whether NMP, compared with SCS, exerts a protective effect on the glycocalyx.[22] Further studies are needed to investigate the influence of NMP compared with SCS on endothelial glycocalyx and the influence of glycocalyx damage on organ function and long-term patient outcome.

Another important finding of this study was that patients in the NMP after SCS group needed significantly less substitution of fibrinogen concentrate compared with patients of the SCS group. Fibrinogen is the substrate for plasmatic hemostasis and is the first factor reaching critical levels during massive bleeding, even before platelets and factors of the prothrombin complex.[23] Therefore, it could be argued that the lower amount of blood loss in patients of the NMP after SCS group contributed to this finding. In contrast, fibrinogen

is synthesized by the liver.[24] Because lower AST values were observed in the recipients after NMP in our as well as in previous studies, probably because of less damage of the graft compared with SCS, it could be hypothesized that the lower need for fibrinogen substitution may indicate a more rapid onset of fibrinogen synthesis after graft reperfusion in the recipient.[5] However, further studies are needed to investigate the mechanism behind this finding.

Interestingly, compared with previous studies assessing the effect of NMP, we did not find reduced catecholamine requirements after NMP after SCS and a reduced incidence of PRS after NMP after SCS.[5,9] In fact, the incidence of PRS according to the definition of Aggarwal was very low in our patient collective (11.1%).[11] Our results, however, are in line with a recent study from Ceresa et al,[13] who analyzed the incidence of PRS after SCS followed by NMP of a liver graft. In their cohort, only 10% of patients developed a PRS, which is comparable with our data. In general, the reported incidence of PRS is much higher in the literature and the reason for our contradictive findings is unclear.[25-27] It can only be hypothesized that preventative measures, such as increased catecholamine support already before mean arterial pressure decreased to levels compatible with the definition of a PRS, may have prevented the development of a real PRS in our and other studies of patient cohorts.

Our study has several limitations. First, the liver transplant recipients represent a very heterogeneous collective.[28,29] Despite matching according to the reported parameters, comorbidities of the patients showed considerable variation, which may lead to distortions, especially in a small cohort. Because of the relatively small size of the NMP group, there is a certain risk of insufficient statistical power, which may explain why although the occurrence of PRS was seen more often in the SCS group, the difference did not reach statistical significance. The small group size is probably the most important limitation of this study. Because the anesthesiological approach in our hospital has now markedly changed toward a "low volume technique," the liver transplantations now performed are no longer comparable with those in this study.[30] Third, because of the retrospective character of this study several confounding factors may have influenced our findings.

CONCLUSION

Our data indicate that NMP in a back-to-base approach has a beneficial effect on transfusion requirements of RBCs, PCs, and fibrinogen concentrate compared with standard SCS. Prospective studies with larger patient cohorts are needed to confirm these findings and further elucidate the pathophysiology behind NMP.

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