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BRIEF COMMUNICATION

Reducing cold ischemia time by donor liver "back-table" preparation under continuous oxygenated machine perfusion of the portal vein

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Abstract

Introduction: Cold ischemia time is a well-known risk factor for the development of non-anastomotic biliary strictures (NAS) after liver transplantation. End-ischemic hypothermic oxygenated machine perfusion (HOPE) of DCD liver grafts reduces the incidence of NAS, and has the potential to reduce cold ischemia times. We hypothesized that if a part of the back-table procedure could be performed under continuous HOPE, cold ischemia times would be reduced.

Methods: In this prospective observational cohort study, all nationwide declined livers that underwent DHOPE-NMP between July 1st 2021 and January 1st 2022 were included. The back-table of ten consecutive high-risk donor livers was performed with ongoing HOPE. Sixty DHOPE-NMP procedures (August 1st 2017–July 1st 2021) with a conventional back-table procedure functioned as a control group.

Results: Compared to the control group, this technique led to a decrease in non-oxygenated back-table time from median 74 min (IQR 58–92 min) to median 25 min (IQR 21–31 min), $p < .01$. Median total cold preservation times were reduced from 279 min (IQR 254–297) to 214 min (IQR 132–254), $p < .01$.

Conclusion: Cold ischemia time of liver grafts can be successfully reduced by over one hour by using portal vein only HOPE during back-table preparation.

KEYWORDS
cold ischemia time, liver, machine perfusion

1 | INTRODUCTION

The success of liver transplantation is strongly inhibited by the scarcity of donor organs. This has resulted in a major increase in the use of donation after circulatory death (DCD) donor livers. However, DCD livers are more susceptible to severe post-transplant complications, such as primary graft non-function and post-transplant cholangiopathy.[1] Among the post-transplant cholangiopathies, the non-anastomotic strictures (NAS) of the biliary tree are the most infamous, which often necessitate multiple endoscopic interventions and can result in even re-transplantation or patient death.[1] One of the most important risk factors for the development of NAS after liver transplantation is the

length of the cold ischemia time (the time between donor in situ cold flush and the start of implantation in the recipient).[1,2] As there is a detrimental cumulative effect between donor age and length of cold ischemia time on the development of NAS, the use of older DCD livers has been associated with high incidences of NAS.[1] As a consequence, many centers avoid using donor livers from DCD donors who are over the age of 60 years for transplantation.

All DCD livers in our center undergo dual hypothermic oxygenated machine perfusion (HOPE),[3] and only high-risk DCD livers (including those from donors aged >60 years) subsequently undergo normothermic machine perfusion (NMP) for viability assessment, necessitating arterial perfusion.[4] Recently, we reported the outcomes after combined HOPE and NMP for high-risk DCD livers (69% of donors aged >60 years).[4] A 69% utilization rate was achieved, with a 100% 1-year graft survival after transplantation.[4] As expected, a significant difference between the viable (270 min) and non-viable livers (326 min; $p = .018$) was the length of the cold ischemia time.

We have attempted to reduce cold ischemia times by increasing awareness among local organ procurement teams.[2] However, we observed that a substantial part of the cold ischemia time took place in our own center during back-table preparation of the organ prior to initiation of machine perfusion. DCD livers are often procured en-bloc with the pancreas. The ex situ splitting of the pancreas from the liver during the back-table procedure, including dissection and preparation of the common hepatic artery and potentially performing reconstruction of aberrant hepatic arteries, as well as cannulation of the liver vasculature, requires a substantial amount of time. Of 60 consecutive machine perfusion procedures in our center, the median back-table time required to prepare the organ for machine perfusion and subsequent transplantation was 74 min (interquartile range [IQR] 58–92). This was responsible for a substantial amount of the total cold ischemia time (median of 279 min; IQR 254–297 min).

Reducing the cold ischemia times for grafts requiring arterial reconstruction has previously been described by Nasralla et al.[5] They performed the arterial reconstruction of five liver grafts during ongoing NMP. However, NMP requires cannulation of the hepatic artery to prevent warm ischemia of the biliary tract. Oxygenated perfusion in a hypothermic environment does not require dual perfusion, providing the opportunity to reduce cold ischemic times with portal vein HOPE only.

We hypothesized that if a part of the back-table procedure could be performed under continuous single vessel (portal vein) HOPE, cold ischemia times would be reduced.

2 | METHODS

In this prospective observational cohort study, all nationwide declined livers that underwent sequential DHOPE-NMP over a time span of 6 months (July 1st 2021–January 1st 2022) were included. In the study group, a substantial part of the back-table procedure was performed with continuous HOPE. The primary endpoint was the reduction in the total cold ischemic time. All livers included in this study were compared with a contemporary cohort of preceding, consecutive DHOPE-NMP procedures (August 1st 2017–July 1st 2021) where the back-table procedure was performed in the conventional manner.

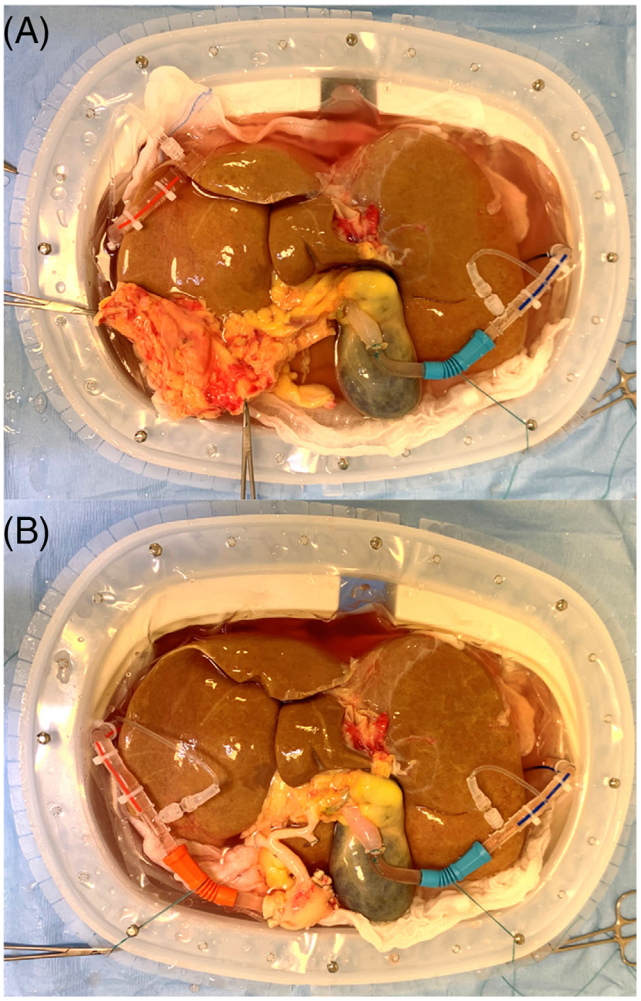

FIGURE 1 Back-table procedure of a large, steatotic liver (2931 grams) under continuous single vessel (portal vein) hypothermic oxygenated machine perfusion (HOPE). (A) After initiation of HOPE, hilar dissection is continued with the identification and dissection of the arterial branches, as well as removal of hilar fat and lymph nodes. A gauze is placed underneath the liver to prevent debris entering the perfusion system. (B) After completion of the "back-table procedure," dual HOPE through both the portal vein and hepatic artery is commenced.

Upon arrival of the donor liver in our center, the back-table procedure was commenced by removing the remainder of the adherend diaphragm and dissection of the inferior vena cava, followed by dissection of the extrahepatic portal vein from the pancreatic head. As soon as the portal vein was separated from surrounding tissue, a regular 25Fr angled cannula (Figure 1A) was introduced and secured. According to our local DHOPE protocol, the liver was subsequently flushed with at least 1L of University of Wisconsin machine perfusion solution (Belzer MPS, Carnamedica, Warshaw, Poland).[3]

The liver was then transferred to the machine perfusion device (Liver Assist, XVIVO, Gothenburg, Sweden). A large gauze was placed

TABLE 1 Donor characteristics and organ preservation times

	Back-table with HOPE 10 DHOPE-NMP	Regular back-table 60 DHOPE-NMP	*p*-Value
Age (years)	64 (60-71)	66 (56-71)	.83
Donor agonal phase[a] (min)	16 (10-29)	16 (11-20)	.88
Donor asystolic phase[b] (min)	18 (16-19)	16 (15-18)	.19
Functional donor warm ischemia time[c]	28 (22-44)	30 (25-33)	.70
Donor type	DBD: 0 DCD: 10	DBD: 2 DCD: 58	.56
Donor risk index[d]	2.83 (2.49-3.22)	2.85 (2.51-3.18)	.50
Non-oxygenated back-table time (min)[e]	25 (21-31)	74 (58-92)	<.01
Oxygenated back-table time (min)[f]	36 (27-51)	–	–
Total cold ischemia time (min)[g]	214 (132-254)	279 (254-297)	<.01
Utilization rate (%)	90	62	.09

Abbreviations: DBD; donation after brain death, DCD; donation after circulatory death, DHOPE; dual hypothermic oxygenated machine perfusion HOPE; hypothermic oxygenated machine perfusion.
[a]Time between withdrawal of life support and circulatory arrest.
[b]Time between circulatory arrest and start of in situ cold flush.
[c]Time from donor saturation <80% or mean arterial pressure <60 mmHg to initiation of in situ cold flushing in the donor.[10]
[d]Validated scoring tools to assess the risk of liver graft failure.[11]
[e]Time between start of regular back-table procedure and flushing of the portal vein.
[f]Length of HOPE prior to DHOPE.
[g]Time between start of in situ cold flush and beginning of (D)HOPE.

under the liver to prevent tissue/debris from entering the liver reservoir and perfusion circuit (Figure 1A). Target portal vein flow was between 150 and 250 ml/min with pressures ≤5 mmHg and an oxygenation >106 kPa, as measured with an arterial blood gas analyzer (ABL90 FLEX PLUS, Radiometer Medical ApS, Brønshøj, Denmark).[3,6] After initiation of HOPE, the hilar dissection was continued by dissection of the pancreatic head and preparation of the coeliac trunc and common hepatic artery (Figure 1A). After closure of all arterial side-branches, and potential reconstruction, a regular 25Fr cannula was placed in the supratruncal aorta, and the infratruncal aorta was closed with a running suture. Hereafter, the cannula in the supratruncal aorta was connected to the arterial perfusion system, and dual HOPE was commenced according to previously reported protocols (Figure 1B).3 During the machine perfusion procedure, always one perfusionist was present to re-adjust perfusion settings if manipulation of the liver during the back-table resulted in portal flow changes or pressure alarms.

Continuous data are presented as median (IQR), whereas categorical data are presented as number (percentage). Continuous variables were compared using the Kruskal-Wallis test, categorical variables with the Chi-Square test or Fisher's Exact test where appropriate.

3 | RESULTS

In total, ten livers were included in this study (Table 1), whereas sixty DHOPE-NMP procedures were performed with the conventional method. All livers were donated after circulatory death, with a median donor age of 64 years (IQR 60–71). The median functional warm ischemia time was 28 min. The donor risk index in both groups was >2.50, demonstrating the high-risk profile of these livers. In all ten livers, within 14–38 min after initiation of the back-table procedure, the portal vein was flushed, and the liver was connected to the machine perfusion device. The median time required to connect the hepatic artery to the perfusion device after the start of HOPE was 36 min (Table 1).

An organ perfusionist was present to closely monitor the portal perfusion flow during the preparation of the hepatic artery. Device alarms during HOPE did not occur. However, the perfusion flow through the portal vein occasionally decreased by manipulation of the portal vein during hepatic artery preparation. Stopping this manipulation whenever possible for hepatic artery preparation restored the original flow in all cases without interventions.

When comparing the results from these ten livers with the control group of livers that underwent a regular back-table procedure, the median non-oxygenated back-table time, was significantly reduced for the livers that underwent a back-table with HOPE compared to the regular back-table procedure (25 min [IQR 21–31] vs. 74 [IQR 58–92] min, $p < .01$) (Table 1). Subsequently, the total cold ischemia times, the primary endpoint, were also reduced from median 279 min [IQR 254–297] to median 214 min [IQR 132–254], $p < .01$ (Table 1). The utilization rate was higher in the HOPE back-table group than in the conventional back-table group, but this did not reach statistical significance (90% vs. 62%, $p = .09$).

4 | DISCUSSION

In this study, we present a proof-of-concept that a back-table procedure of a donor liver is feasible to perform with ongoing HOPE. We show that the cold ischemia time can be reduced by at least one hour if a donor liver receives HOPE via the portal vein during the back-table procedure. This technique has the potential to improve transplant outcomes, as cold ischemia times are strongly associated with post-transplant complications, including development of non-anastomotic biliary complications.[6,7]

The detrimental effect of cold ischemia times on hepatobiliary function has been studied extensively. Cold ischemia times exceeding four hours have been associated with an increased incidence of graft loss and ischemic cholangiopathy.[7] Other studies using high-risk DCD grafts aim for a cold ischemia time below five hours.[6] While most of the cold ischemia time occurs during organ procurement and transport, a significant part comprises the preparation of the donor liver for transplantation during the back-table procedure in the recipient center. Our aim was to develop a technique to reduce the cold ischemia time during the back-table procedure. Unlike NMP, hypothermic machine perfusion can be performed safely via single vessel (portal vein) perfusion only.[8,9] This allows for a short non-oxygenated back-table procedure for portal cannulation. Hereafter, the back-table procedure can be continued under continuous HOPE via the portal vein, with hilar dissection of the hepatic artery and removal of hilar fat tissue, lymph nodes and/or pancreas tissue. Especially in the case of aberrant arterial anatomy, which occurs in up to 30% of donor livers, we have experienced that by performing HOPE, the arterial dissection and potential reconstruction can be performed in a setting with less time pressure, not only shortening cold ischemia time but also providing a benefit to the quality of the back-table procedure. With maximal cold ischemia times ranging between four and five hours for high-risk DCD livers, a 65 min reduction of total cold ischemic time is significant and potentially makes the difference between successful and not successful transplantation of high-risk DCD livers, although this remains to be established.

A limitation of this study is that due to the observational design, any residual bias cannot be excluded. Another limitation is the relatively small numbers in the intervention group. Potentially with larger groups, the difference in utilization rate would have reached statistical significance. Based on the proof-of-concept provided in this study, performing the back-table preparation under continuous HOPE has been introduced as standard of care in our transplant center. This results in reduced cold ischemia times and in more educational opportunities as the time pressure is reduced during the oxygenated back-table procedure.

In conclusion, the "back-table on the pump" procedure results in a reduction of cold ischemic time of over 1 h in comparison to the conventional back-table procedure. We propose to perform the back-table procedure of donor livers "on the pump," under continuous portal vein perfusion, to take maximal advantage of HOPE to reduce the cold ischemia time, especially for DCD livers.

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CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

VAL, CIB, RJP, VEdM, OBvL contributed to study design and data collection. VAL and OBvL wrote the manuscript. CIB, RJP and VEdM critically revised the manuscript.

DATA AVAILABILITY STATEMENT

Data is available upon reasonable request.

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