Transplantation of Suboptimal Donor Livers: Exploring the Boundaries

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Appendix I: First Report of Successful Transplantation of a Pediatric Donor Liver Graft after Hypothermic Machine Perfusion

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ABSTRACT

One of the main limiting factors in pediatric liver transplantation is donor availability. For adults, donation after circulatory death (DCD) liver grafts are increasingly used to expand the donor pool. To improve outcome after DCD liver transplantation, *ex situ* machine perfusion is used as an alternative organ preservation strategy, with the supplemental value of providing oxygen to the graft during preservation. We here report the first successful transplantation of a pediatric DCD liver graft after hypothermic oxygenated machine perfusion.

The full size liver graft was derived from a 13-year-old, female DCD donor and was end-ischemic pre-treated with dual hypothermic oxygenated machine perfusion. Arterial and portal pressures were set at 18 and 4 mmHg, slightly lower than protocolized settings for adult livers**.** During 2 hours of machine perfusion, portal and arterial flows increased from 100 to 210 ml/min and 30 to 63 ml/min respectively. The pre-treated liver graft was implanted in a 16-year-old girl with progressive familial intrahepatic cholestasis type 2. Postoperative aspartate aminotransferase, alanine aminotransferase and prothrombin time normalized within a week. The recipient quickly recovered and was discharged from the hospital after 18 days. One year after transplantation she is in excellent condition with a completely normal liver function and histology.

This case is the first report of successful transplantation of a pediatric DCD liver graft after hypothermic oxygenated machine perfusion and illustrates the potential role of *ex situ* machine perfusion in expanding the donor pool and improving outcome after pediatric liver transplantation.

INTRODUCTION

Orthotopic liver transplantation is the only effective therapy in patients with end-stage liver disease. Still, donor availability is the main limiting factor in liver transplantation, especially in pediatric patients, who need a perfect size-appropriate graft.[1] To expand the number of suitable liver grafts for pediatric recipients, several technical variants are practiced, including splitting of deceased adult donor liver grafts and the use of living donors. Despite this, waiting list mortality rate is up to 20%.[2] Moreover, during the period on the waiting list children are at great risk of growth and developmental retardation.

For adults, donation after circulatory death (DCD) liver grafts are increasingly used to expand the donor pool. Good results with transplantation of DCD liver grafts are reported, but a major concern remains the high rate of biliary complications. For children, the use of DCD grafts is still controversial and the available data are limited to small series.[3,4]

To improve outcome of DCD liver transplantation, *ex situ* hypothermic machine perfusion (HMP) is increasingly used as an alternative strategy for organ preservation, with the supplemental value of providing oxygen to the graft during preservation.[5] The initial experience in adults has demonstrated that end-ischemic HMP provides better preservation of DCD liver grafts. HMP ameliorates ischemia-reperfusion injury in DCD liver grafts by restoring mitochondrial function before implantation and it offers better preservation of the bile ducts and their vasculature.[6,7] This is an important step forward in reducing biliary complications after DCD liver transplantation.

So far, machine perfusion has only been reported in adult to adult liver transplantation. We here report the first successful transplantation of a pediatric DCD liver graft after oxygenated HMP.

CASE PRESENTATION

The liver graft was derived from a 13-year-old, female DCD donor (65 kg, 167 cm), who was resuscitated after an out of hospital cardiac arrest. She was admitted to the intensive care unit for 7 days. Last serum alanine aminotransferase before procurement was 65 U/L, last serum sodium was 162 mmol/L. The agonal phase between withdrawal

from life support until circulatory arrest was 19 minutes. After a mandatory 5 minutes 'no touch period', rapid cannulation of the aorta was performed and the liver was *in situ* perfused with ice-cold Belzer University of Wisconsin (UW) cold storage solution (supplemented with heparin). The total period from withdrawal of life support to *in situ* cold perfusion endured 34 minutes. The bile ducts were gently flushed in a retrograde fashion with UW preservation solution. Subsequently, the liver was packed static cold storage and transported to our center.

In our center the liver graft was inspected and appeared to be of good quality. Liver weight was 1509 gram. Because the liver was derived from a DCD donor and to minimize further ischemic injury as much as possible, it was decided to prepare the liver graft for oxygenated HMP during recipient hepatectomy. A conventional back table procedure of the graft was performed after which the portal vein and supratruncal aorta were cannulated for machine perfusion. Subsequently, the liver underwent pressure-controlled dual hypothermic oxygenated machine perfusion using the Liver Assist (Organ Assist, Groningen, The Netherlands). The perfusion fluid consisted of 4000 mL Belzer UW machine perfusion solution, supplemented with 3420 mg glutathione. Perfusion fluid was oxygenated with 1 L/min 100% O2 to obtain a PaO2 of >70 mmHg and temperature was kept at 10 °C, according to our HMP protocol.[6] Arterial and portal pressures were set at 18 and 4 mmHg respectively, which is slightly lower than our protocolized settings for adult livers (25 and 5 mmHg respectively). During HMP portal flow increased adequately from 100 to 210 ml/min and arterial flow from 30 to 63 ml/min, whereas pressure and temperature remained stable (Figure 1). Perfusate glucose level increased in the first 30 minutes of HMP from 8.8 to 12.5 mmol/L, and remained stable thereafter. The perfusate lactate level decreased from 2.4 to 1.7 mmol/L. After 2 hours of HMP the liver was disconnected from the perfusion machine and transplanted.

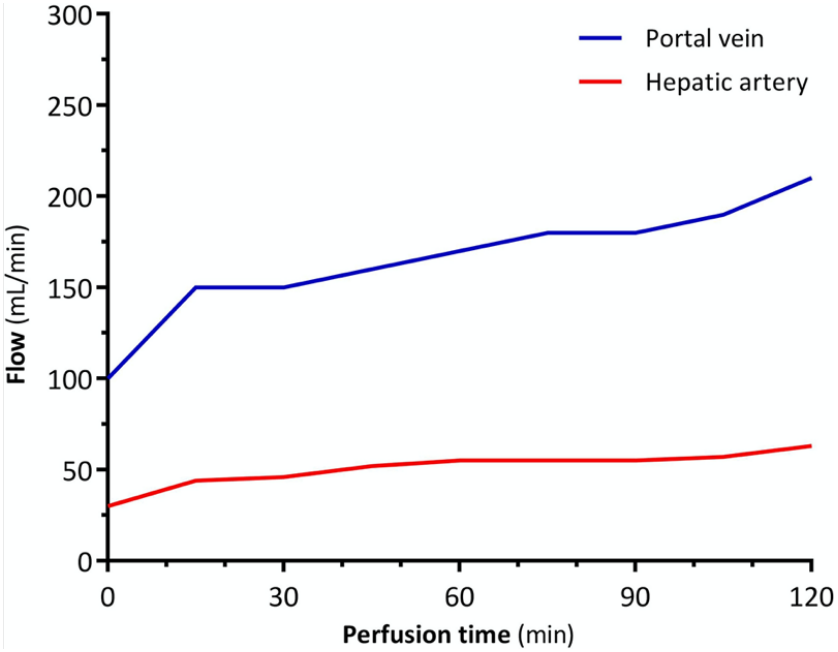

Figure 1. Portal and arterial flow rates during two hours of dual hypothermic oxygenated machine perfusion of an 13-year-old DCD liver graft.

The perfusion machine was pressure-controlled with portal pressure set at 4 mmHg and arterial pressure set at 18 mmHg. DCD, donation after circulatory arrest.

The selected recipient was a 16-year-old girl (42 kg, 156 cm), who was diagnosed in the neonatal phase with progressive familial intrahepatic cholestasis type 2. To prevent progressive damage of the hepatocytes by retention and accumulation of bile salts, a partial external biliary diversion procedure was performed when she was 4 years old.[8] Despite this, at the age of 14 years she was listed for liver transplantation because of deterioration of cholestasis with icterus and itching, and bile stoma bleedings. The recipient and her parents gave consent to receive a HMP-preserved DCD liver.

The HMP-pretreated full size liver graft was implanted using the piggyback technique with end-to-end portal and arterial anastomoses. Perioperative blood loss was 1800 ml and the recipient received one red blood cell transfusion (280 ml) intraoperatively. Total cold preservation time of the donor liver graft was 512 minutes, consisting of 384 minutes of cold ischemic storage and 128 minutes of oxygenated HMP. Subsequent warm ischemia time was 33 minutes. Immediately after transplantation the recipient was extubated and admitted to the pediatric intensive care unit where vasopressive support could be reduced to zero and intravenous heparin was administered as is

routine practice after pediatric transplantation in our center. Postoperative aspartate aminotransferase, alanine aminotransferase and prothrombin time rapidly decreased and normalized within a week (Figure 2a). Alkaline phosphatase and gamma-glutamyl transferase normalized within a month and remained stable afterwards. Immediate postoperative lactate was 3.5 mmol/L and levels steadily decreased thereafter, with a small second peak on postoperative day 4 when an intra-abdominal bleeding was diagnosed which required surgical intervention (Figure 2b). Surgical inspection showed diffuse oozing with a potential bleeding focus at the inferior vena cava which was clipped and additionally a hematoma was evacuated. After this, the recipient had a quick and further uneventful recovery until she was discharged from the hospital on postoperative day 18. One year later, the recipient is in excellent condition with a completely normal liver function with a serum alanine aminotransferase of 16 U/L, bilirubin of 7 μmol/L and a normal liver histology on routine liver biopsy. There were no clinical or histological signs of biliary complications, additional imaging was not performed.

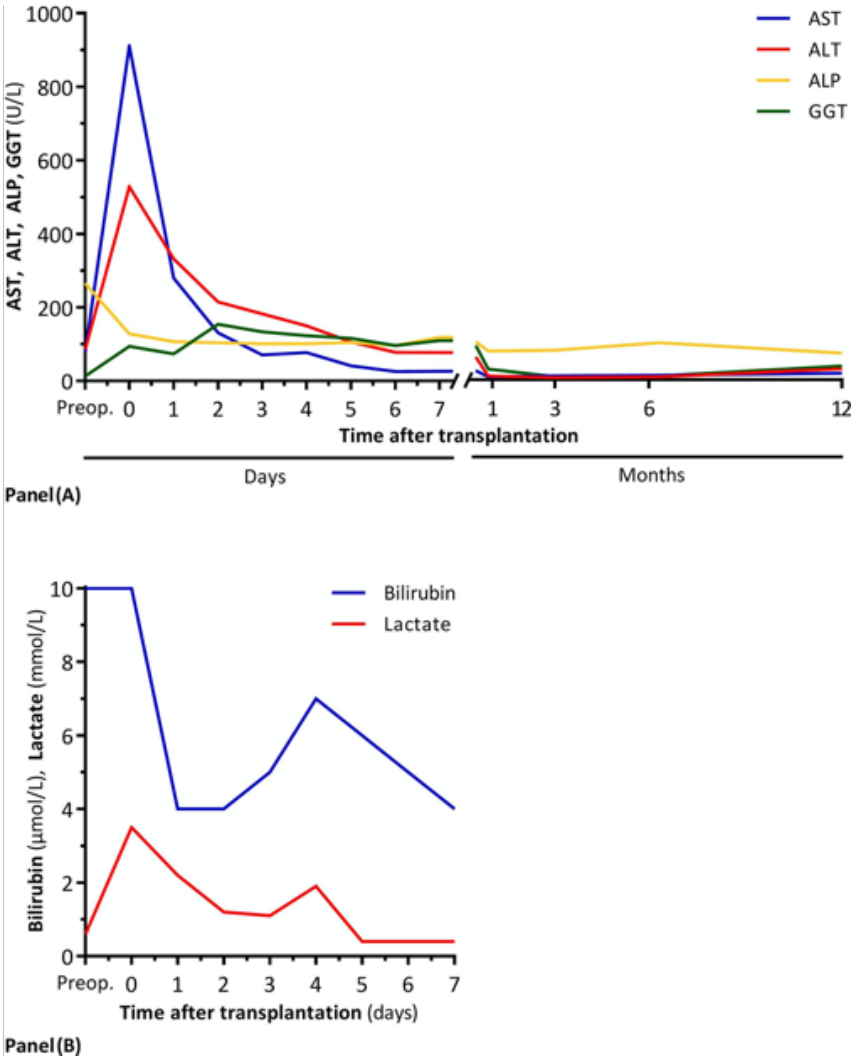

Figure 2. ***Panel A:*** *Serum AST, ALT, ALP and GGT levels in a 16-year-old recipient after successful transplantation of a hypothermic oxygenated machine perfused pediatric DCD liver graft.* ***Panel B:*** *Serum bilirubin and lactate in a 16-year-old recipient after successful transplantation of a hypothermic oxygenated machine perfused pediatric DCD liver graft. AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; DCD, donation after circulatory arrest.*

DISCUSSION

This case report describes the first successful transplantation of a pediatric DCD liver graft after *ex situ* oxygenated HMP. There are only a few descriptions of pediatric liver transplantations with grafts from DCD donors in the current literature.[3,4,9] Hong et al. reported a matched case-control study of 7 DCD liver transplantations in pediatric patients with excellent long-term outcomes.[3] A biliary anastomotic stricture occurred in

only one of the recipients and the incidence of biliary complications was not different between DCD and donation after brain death liver transplantations. Also Gozinni et al. have suggested that liver grafts from young DCD donors with short ischemia times can be safely used in pediatric transplantation.[9] Moreover, van Rijn et al. demonstrated that transplantation of pediatric DCD liver grafts results in good long-term outcomes, when the donor warm ischemia time is kept under 30 minutes.[4] Patient- and graft survival rates were comparable to those of pediatric donation after brain death liver grafts. Moreover, the incidence of non-anastomotic biliary strictures after transplantation of pediatric DCD livers was remarkably low. These studies support the use of pediatric DCD liver grafts for transplantation.

A major drawback of DCD liver grafts is the devastating effect of warm with subsequent cold ischemia, leading to depletion of intracellular energy sources, such as adenosine 5'-triphosphate, combined with other metabolic disturbances. This results into cellular injury and dysfunction due to reperfusion injury during transplantation.[10,11] Ischemia-reperfusion injury is a major cause of primary non function, early allograft dysfunction and biliary complications after transplantation.[12]

In adult liver transplantation, it has been demonstrated that a short period (1-2 hours) of oxygenated HMP after traditional static cold storage restores the hepatic energy status in liver grafts, reduces ischemia-reperfusion injury, and improves early graft survival.[5,6,13] Based on these experiences, we decided to apply end-ischemic HMP to the pediatric DCD liver graft offered to our recipient. Compared to adult liver grafts, pediatric livers are smaller and potentially more susceptible to intravascular pressure-induced damage. This is important because one of the potential risks of HMP is endothelial injury due to shear stress. Shear stress occurs in case of high perfusion pressures, especially at low temperatures when endothelial cell membranes are susceptible to injury.[14] Perfusion induced endothelial cell injury can be prevented by using low perfusion pressures and a pressure-controlled perfusion system.[13,15] Therefore, we used a pressure-controlled machine perfusion device with arterial and portal perfusion pressures lower than values generally used for adult liver grafts.[16]

In the reported case we demonstrated HMP of a 13-year-old DCD liver graft, which is relative large. To determine optimal portal and arterial pressures for HMP in pediatric liver grafts, more experiences and research are required. In our opinion, perfusion pressures in pediatric liver grafts, should be lowered based on donor age, to adjust for

the lower physiological pressure in the liver graft. For HMP in adult liver grafts, protocolized portal and arterial perfusion pressures are set at 3-5 and 25 mmHg respectively.[6,13] Normally, an adult liver graft is used to a physiological mean arterial blood pressure of 90 mmHg in the donor, whereas pediatric liver grafts are used to lower systemic blood pressures. Perhaps we should lower perfusion pressures for pediatric liver grafts based on donor mean arterial blood pressures according to donor age. For example, a 5-year old pediatric liver graft, is used to a mean arterial blood pressure of 65 mmHg, which is about 30% lower when compared to 90 mmHg in adults. Therefore it seems reasonable to reduce the portal and arterial pressure with 30%, leading to a portal and arterial perfusion pressure of 3-4 and 18 mmHg during HMP, respectively.

In the coming years, further advances in organ preservation, such as machine perfusion may provide a solution to the problem of donor organ scarcity for pediatric patients. Machine perfusion of DCD donor grafts might reduce part of the risks of DCD liver transplantation. With this case we demonstrated that HMP of a pediatric liver graft is feasible and can be performed safely with adjusted perfusion pressures.

Apart from providing a better preservation method, machine perfusion can also facilitate pediatric liver transplantation by enabling a split procedure of a liver graft under continuous oxygenated perfusion. The concept of splitting a liver graft during machine perfusion was recently shown by Stephenson et al.[17] These investigators successfully performed a split procedure of an adult liver graft resulting in a segment 2/3 and an extended right lobe graft. In addition, with the upcoming technique of normothermic machine perfusion, which enables *ex situ* functional assessment of the liver graft prior to implantation, it might be useful to estimate the suitability of a suboptimal liver graft for a pediatric recipient.[18] Altogether, this may increase the number of liver grafts that are suitable for pediatric liver transplantation.

In conclusion, we present the first successful transplantation of a pediatric DCD liver graft after *ex situ* hypothermic oxygenated machine perfusion. This case illustrates the potential role of *ex situ* machine perfusion technology in expanding the donor pool and improving outcome after pediatric liver transplantation.

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Appendix II: Viability criteria for functional assessment of donor livers during normothermic machine preservation

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Persisting donor organ shortage has led to an increased use of suboptimal donor livers for transplantation. Transplantation of these extended criteria donor (ECD) livers, however, is associated with high rates of complications, including early allograft dysfunction (EAD) and primary non-function (PNF). As a result, a large number of ECD livers are discarded. The decision to accept or decline an ECD liver for transplantation is largely based on empiric and rather subjective criteria available at the time of donor organ offer, but it may not reflect the actual condition of an organ after several hours of static cold storage (SCS). Ex situ machine perfusion is increasingly being studied as a method to resuscitate and functionally assess donor organs shortly before transplantation. When performed at 37°C, ex situ normothermic machine perfusion (NMP) enables a metabolic assessment of high-risk liver grafts. However, there is currently no consensus on the criteria that can be used during NMP to select liver grafts that can be transplanted safely, despite initial decline based on an estimated too high of a risk for EAD/PNF.

In this issue of *Liver Transplantation*, Mergental et al. report an interesting study in which they aimed to identify criteria that can be used during NMP to predict PNF of high-risk donor livers.[1] A total of 12 discarded human donor livers underwent NMP using a perfusion solution based on packed red blood cells for up to 6 hours after a period of SCS. Perfusate blood gas profiles, bile production, and vascular flow characteristics were examined to identify parameters that are associated with poor liver function and a high degree of injury on histology of liver biopsies. Initially, the authors identified lactate clearance as a marker for graft viability. The authors observed 2 distinct groups: a group of 6 organs with a sharp decrease in lactate levels, whereas the other 6 showed "fluctuations and rises" of the lactate levels in the perfusion solution.

After this observation, further analyses were performed by comparing these lactate-clearing and nonlactate- clearing groups. Second, the authors noted less hepatocellular injury on histology, higher hepatic adenosine triphosphate levels, more stable perfusate pH, and higher bile production in the lactate-clearing group compared with the nonlactate-clearing group. These findings supported their use of lactate as an indicator of hepatocellular function and corroborates previous results from other groups.[2,3] Bile production, however, was observed in only 4 of the 6 livers in the lactate-clearing group

versus 1 out of 6 livers in the nonlactate-clearing group. The authors conclude that measurable bile production can be used as a marker of good liver function, but the absence of bile production does not necessarily imply poor function. Similar observations have been made by transplant groups from Cambridge and Cleveland.[2,3]

In our experience, we have noted that very low or absent bile flow can sometimes be explained by a technical issue. For example, the tip of a biliary catheter can be stuck against the bile duct wall obstructing its lumen and precluding bile flow. In addition, we have noted that bile flow through a biliary drain is dependent on the size of the drain. If the diameter of the drain is too large, bile flow may not commence easily, especially as the drain often makes an uprising loop at the rim of the reservoir (Fig. 1B,C in the current article). The use of a small feeding tube catheter (8-Fr) with an open tip and side holes may minimize the risk of these technical issues in measuring bile production. A small-sized catheter provides a capillary force, which facilitates bile flow. These potential issues should be considered when livers seem to produce minimal or no bile despite biochemical evidence of good functional recovery, such as a decreasing lactate level.

Collection of bile produced during NMP is important because it may aid in the assessment of bile duct viability during NMP.[4] This is a topic not covered in the current study by Mergental et al., but it is clinically very relevant, especially in the assessment of high-risk livers from donation after circulatory death (DCD). DCD liver grafts not only have an increased risk of hepatocellular dysfunction that may lead to EAD or PNF, but they are also prone to cholangiopathy due to cholangiocellular injury.[5] Experimental and preclinical studies have indicated that biliary pH, bicarbonate, and lactate dehydrogenase during NMP may reflect biliary viability.[4] Cholangiocytes (biliary epithelial cells) actively modify bile composition by secretion of bicarbonate and resorption of glucose, resulting in an alkalotic pH and low glucose level in bile at the level of the common bile duct. Observations made by the Cambridge group during clinical application of NMP recently supported the potential value of biliary pH in the assessment of biliary viability (and thus the risk of posttransplant cholangiopathy) during NMP.[2] However, more research will be needed to establish the diagnostic accuracy of bile composition in assessing biliary viability. Identification and validation of

biomarkers and criteria of bile duct viability during NMP would be an important step forward in the wider use of DCD liver grafts.

Interestingly, Mergental et al. noted an increase in injury of the intrahepatic small bile ducts during NMP in all but 1 of the livers in the nonlactate-clearing group and in 2 of the 6 in the lactate-clearing group. Altogether, approximately 50% of the livers suffered an increase in biliary injury during NMP. Unfortunately, histological data on the large intrahepatic and or extrahepatic bile ducts were not available. Typically, these larger bile ducts are at risk of ischemia/reperfusion injury, resulting in posttransplant cholangiopathy.[5] Although NMP may mitigate ischemia/reperfusion injury due to the absence of leukocytes and platelets in the perfusion fluid, injury due to the formation of radical oxygen species (ROS) may still occur. In fact, the first clinical studies of liver NMP have not shown a reduction in the incidence of biliary complications after transplantation compared with SCS.[2,6] To improve results, preceding NMP by oxygenated hypothermic machine perfusion (HMP) may be more effective as the latter has been shown to resuscitate mitochondria, reduce postreperfusion ROS production and inflammation, and mitigate reperfusion injury of the bile ducts.[7] In accordance with this, 2 preclinical studies using discarded human donor livers have recently shown that a short period of HMP prior to NMP improves metabolic recovery and attenuates oxidative stress and tissue inflammation.[8,9] Therefore, it may be important to sequentially apply HMP and NMP, especially when NMP is used to assess the transplantability of high-risk DCD livers, which in addition to the risk of EAD and PNF have a high risk of developing biliary complications after transplantation. Liver viability testing remains a highly difficult research field as the translation to clinical application must be performed with exceptional care. On the basis of the principle of *primum non nocere*, patient safety has to be the main concern. This concern has forced clinical research groups to remain on the safe side when it comes to transplantation of initially declined livers after a positive viability judgment by NMP. On the other hand, a too prudential application is hampering the identification of clinically relevant cutoff values of viability criteria. With increasing experience, however, it can be expected that centers will start pushing the boundaries by stretching the acceptance criteria. As long as this process is carefully monitored and outcome data are published in a standardized

fashion,[10] we will collectively learn from this process and be able to effectively and safely use the potential benefits of ex situ machine perfusion in increasing the number of suitable organs for transplantation.

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