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In Situ Normothermic Regional Perfusion for Controlled Donation After Circulatory Death—The United Kingdom Experience

G. C. Oniscu[1,*], L. V. Randle[2], P. Muiesan[3], A. J. Butler[2], I. S. Currie[1], M. T. P. R. Perera[3], J. L. Forsythe[1] and C. J. E. Watson[2]

[1]*Transplant Unit, Royal Infirmary of Edinburgh, Edinburgh, UK*
[2]*Transplant Unit, Addenbrooke's Hospital and NIHR Cambridge Biomedical Research Centre, Cambridge, UK*
[3]*Liver Transplant Unit, Queen Elizabeth Hospital, Birmingham, UK*
[*]*Corresponding author: Gabriel C. Oniscu, gabriel.oniscu@ed.ac.uk*

Organs recovered from donors after circulatory death (DCD) suffer warm ischemia before cold storage which may prejudice graft survival and result in a greater risk of complications after transplant. A period of normothermic regional perfusion (NRP) in the donor may reverse these effects and improve organ function. Twenty-one NRP retrievals from Maastricht category III DCD donors were performed at three UK centers. NRP was established postasystole via aortic and caval cannulation and maintained for 2 h. Blood gases and biochemistry were monitored to assess organ function. Sixty-three organs were recovered. Forty-nine patients were transplanted. The median time from asystole to NRP was 16 min (range 10–23 min). Thirty-two patients received a kidney transplant. The median cold ischemia time was 12 h 30 min (range 5 h 25 min–18 h 22 min). The median creatinine at 3 and 12 months was 107 μmol/L (range 72–222) and 121 μmol/L (range 63–157), respectively. Thirteen (40%) recipients had delayed graft function and four lost the grafts. Eleven patients received a liver transplant. The first week median peak ALT was 389 IU/L (range 58–3043). One patient had primary nonfunction. Two combined pancreas–kidney transplants, one islet transplant and three double lung transplants were performed with primary function. NRP in DCD donation facilitates organ recovery and may improve short-term outcomes.

Abbreviations: ALT, alanine transaminase; CIT, cold ischemia time; CVVHD, continuous veno-venous hemo-diafiltration; DBD, donation after brain death; DCD, donation after circulatory death; ECMO, extracorporeal membrane oxygenation; ERCP, endoscopic retrograde cholangio-pancreatography; HCV, hepatitis C virus; IVC, inferior vena cava; NECMO, normothermic extra-corporeal membrane oxygenation (normothermic recirculation); NMP, normothermic machine perfusion; NRP, normothermic regional perfusion; PNF, primary nonfunction; WIT, warm ischemia time

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Introduction

The growing need for organ transplantation has led to a substantial increase in donation after circulatory death (DCD) and higher utilization of extended criteria donor organs. DCD donation represents over 40% of all deceased donation in the United Kingdom (1) and similar figures are seen in other European countries (2). The unpredictable consequences of the warm ischemic injury, which characterizes DCD donation, together with unfavorable hemodynamics during the agonal phase and the often poor perfusion quality, result in a reluctance to use livers and pancreata from these donors, with recovery rates 20–50% lower than from donation after brain death (DBD) donors (1,3).

In the United Kingdom, DCD donation occurs in the context of a patient on an intensive care unit who is deemed to have a catastrophic and nonrecoverable brain injury. Life supporting treatment, including ventilatory support, is withdrawn, followed after a variable time by circulatory arrest. A 5 min period of observation is then required before death can be verified. The donor is transferred to the operating room and, following a rapid laparotomy, organs are perfused *in situ* with cold preservation fluid and removed as quickly as possible.

This process exposes the organs to a period of warm ischemia during the agonal phase after treatment withdrawal and following the circulatory arrest. Subsequent periods of cold ischemia then exacerbate the detrimental effects of warm ischemia, leading to poorer transplant outcomes (1) with a higher incidence of primary nonfunction (PNF), and increased complications rates, such as delayed graft function in kidney transplantation (4) and ischemic cholangiopathy in liver transplantation (5).

One potential way to minimize the ischemic injury and reduce the complication rate following transplantation of

DCD donor organs is to restore circulation with oxygenated blood to the abdominal organs *in situ*, using extra-corporeal membrane oxygenation (ECMO) at body temperature. The use of ECMO to facilitate organ donation was first described in 1997 (6). Normothermic regional perfusion (NRP) (also called normothermic recirculation and normothermic extra-corporeal membrane oxygenation [NECMO]), has been developed in Spain for uncontrolled DCD donors (Maastricht II) (7) where it increased the donor pool. The reported experience indicates low rates of PNF, hepatic artery thrombosis and ischemic cholangiopathy in liver transplantation (8) and a reduction in delayed graft function with good 1-year graft survival in kidney transplantation (9).

ECMO technology has been used sporadically in controlled DCD donation under normothermic (10,11) and sub-normothermic (12) conditions. These reports suggested an increase in recovery rates of extra-renal organs and good initial function. However, a critical factor in these studies has been the ability to administer heparin (in uncontrolled DCD) (7) and perform vascular cannulation and heparinization prior to circulatory arrest (10). Currently in the United Kingdom, neither of these interventions are permitted (13), and therefore, we set to explore if NRP can be undertaken without prior intervention and to investigate its effect on organ recovery rates and transplant function.

Methods

The normothermic extra-corporeal circuits used in this series are shown in Figure 1. The protocols were similar but allowed us to explore different circuit designs, the role of a reservoir and the use of heparin-coated versus noncoated tubing. Accordingly, the circuits were primed using 25 000 units of heparin in Edinburgh where a heparin-coated circuit was used and 50 000 units of heparin in Cambridge and Birmingham (noncoated circuits). Pump flow during NRP was 1.7–4 L/min at 37°C. An oxygen/air mixture was delivered to the oxygenator; no volatile agent was given.

Following withdrawal of treatment and confirmation of death, the donor was transferred to the operating room. A rapid laparotomy was performed and the aorta (or common iliac artery) and the inferior vena cava (IVC) were cannulated. For IVC cannulation, a two stage or three stage venous cannula was used to ensure adequate drainage of the liver and kidneys and avoid the collapse of the cava due to the suction effect of the pump. Thoracotomy was undertaken and the descending thoracic aorta cross-clamped to prevent perfusion of the brain and coronary arteries (13). In the first four cases in Cambridge, the circuit was established via thoracotomy, with cannulation of ascending aorta and the IVC via the right atrium.

NRP was initially established bypassing the oxygenator (and reservoir, where present) to preventing clotting on their large surface area until the heparin in the circuit had mixed with the circulating blood. After 1-min blood flow was diverted through the oxygenator and reservoir, with the intention to continue oxygenated perfusion for 2 h.

Once NRP was established, the bile duct was divided and the gallbladder opened to assess the mucosal appearance and hence the quality of blood perfusion to the liver and biliary epithelium. At the end of the period of NRP, the organs were flushed *in situ* with cold University of Wisconsin preservation solution and removed as in a standard DBD procedure.

NRP monitoring

Abdominal organ function and homeostasis during NRP were monitored every 30 min using blood gases (pH, pO_2, pCO_2, bicarbonate, base excess, lactate), and every 30–60 min for hematology (hemoglobin, hematocrit,

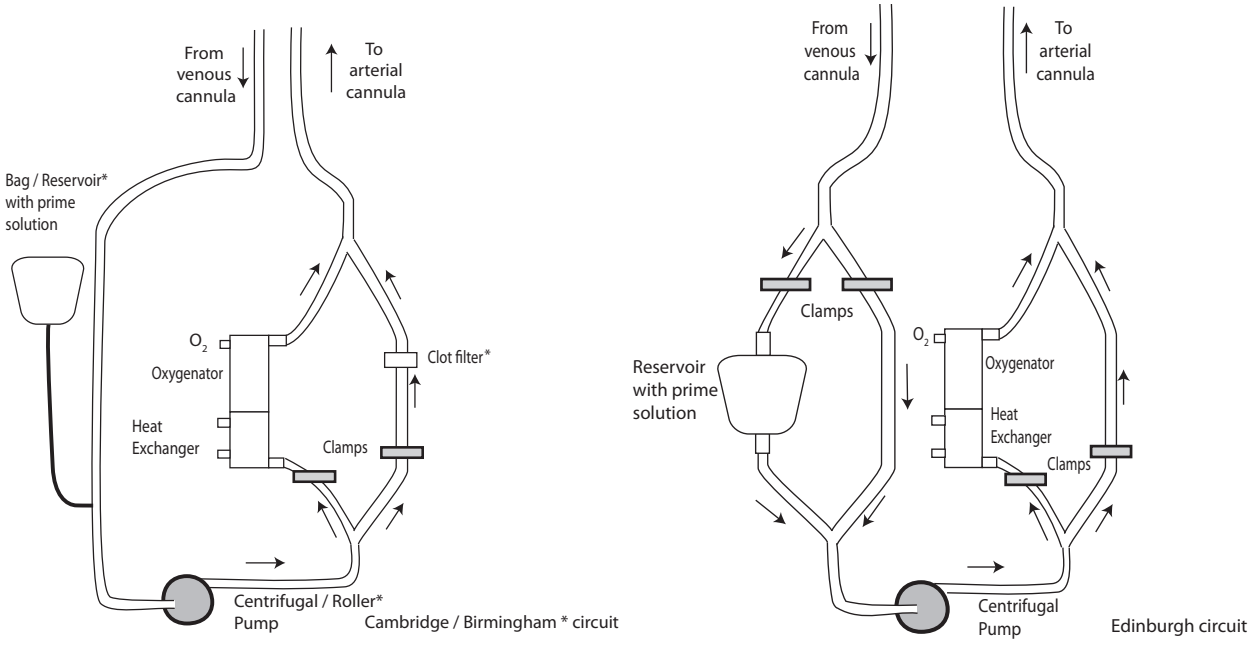

Figure 1: Schematic representation of the *in situ* normothermic regional perfusion circuits (* denotes the variations in the Birmingham circuit: roller pump, clot filter and reservoir).

white cell count, platelet count, activated partial thromboplastin time) and biochemistry (alanine transaminase [ALT], bilirubin, alkaline phosphatase, urea, creatinine, glucose, sodium and potassium).

The protocols at each center varied slightly, but the aim was to maintain a pump flow between 1.7 and 4 L/min, temperature 35.5–37.5°C, pH 7.35–7.45 and a hematocrit >20%. Heparin, 8.4% bicarbonate (as required) and two units of red cell concentrate (range 0–4) were added to maintain these parameters.

The current criteria for DCD selection were observed, with a functional warm ischemia time (WIT; from systolic BP < 50 mmHg to start of perfusion) of less than 30 min for the liver and pancreas, and 1 h for kidneys. In addition, as suggested by the Spanish experience in uncontrolled DCD liver donation, an ALT <3 times the upper limit of normal at the initiation of NRP and <4 times the upper limit of normal at the end of NRP were considered when selecting the liver grafts (7). There were no additional donor exclusion criteria and we attempted NRP in all donors that the teams could attend. Organs were allocated in keeping with the current United Kingdom allocation criteria.

Outcome data

All transplant recipients had a minimum 3-month follow-up. Delayed graft function was defined as the need for dialysis during the first week posttransplant. The cold ischemia time (CIT) was defined as the time from end of NRP to organ reperfusion in recipient.

The outcome for the recipients of NRP kidneys was recorded at 1, 3, 6 and 12 months. For the recipients of NRP livers the incidence of biliary complications, the peak ALT posttransplant, the ALT trend during first postoperative week and the presence of early allograft dysfunction were analyzed. Early graft dysfunction was defined as the presence of one or more of the following: bilirubin ≥10 mg/dL on day 7, international normalized ratio ≥1.6 on day 7 and alanine or aspartate aminotransferases >2000 IU/L within the first 7 days (14).

Results

Twenty-one donors underwent NRP with a further 13 attempts abandoned as the donor did not suffer a circulatory arrest within 4 h of withdrawal of treatment; two additional cases were abandoned due to difficulties in cannulation in the chest and the organs were recovered using a standard abdominal cold perfusion DCD approach. In three donors, lung retrievals were carried out by the cardio-thoracic teams, using cold perfusion while NRP was continued for the abdominal compartment.

The donor demographics are shown in Table 1. The median time from asystole to the start of NRP was 16 min (range 10–23 min) while the median functional WIT was 26 min (range 13–48 min). This included the mandatory 5 min observation period prior to verification of death, and the time taken to transfer the donor to the operating room. The actual time taken for cannulation following skin incision was 7 min (range 5–12 min). Two donors were on veno-venous hemo-diafiltration at the time of retrieval. Individual center organ recovery activity is shown in Table 2.

Sixty-three organs were recovered achieving an organ recovery rate of three organs/donor compared to the national DCD average of 2.6 organs/donor (1). Forty-nine patients received a transplant. The abdominal organ transplant activity is detailed in Table 2.

Table 1: Donor demographics and timings for withdrawal and normothermic perfusion

N = 21 (36 attended)	Donor data median (range)
Age (years)	46 (16–74)
Cause of death	
Cerebrovascular accident	9
Hypoxic brain damage	8
Trauma	3
Respiratory failure	1
Withdrawal to asystole	13 min (6 min–249 min)
Asystole to NRP	16 min (10 min–23 min)
Functional warm ischemia time	26 min (13 min–48 min)
NRP duration	2 h (34 min–2 h 36 min)

NRP, normothermic regional perfusion.

Kidney transplantation

Thirty-two patients received a kidney transplant (4 double) with a median CIT of 12 h 30 min (range 5 h 25 min–18 h 22 min). Overall, 13 recipients (40%) developed delayed graft function (need for dialysis in the first week), of which seven required only a single dialysis episode for hyperkalemia. Four of the recipients with delayed graft function received kidneys from donors who were on hemodiafiltration at the time of retrieval.

Two kidneys were discarded based upon poor preimplantation histology scores as defined by the Remuzzi scoring (15), and four were transplanted as double kidney transplants for the same reason. One kidney was discarded because of a 5 mm smooth muscle tumor of uncertain malignant potential; the contralateral kidney and the liver were transplanted.

The median follow-up was 11 months (range 3–39 months). Serum creatinine levels at 1, 3, 6 and 12 months, are shown in Figure 2.

Table 2: Individual center normothermic regional perfusion retrieval and organ transplant activity

	Number of			
Transplant center	Donors	Livers	Kidneys	Pancreata
Birmingham	3	2	5[1]	–
Cambridge	9	4	16[2]	2
Edinburgh	9	5	17[3]	1[4]
All	21	11	38	3

[1]One donor had a previous nephrectomy.
[2]Three double kidney transplants, two discarded, two combined pancreas and kidney transplants.
[3]One double kidney transplant and one discarded.
[4]One pancreas used for research, one pancreas for islet isolation with insufficient yield and one pancreas used for islets.

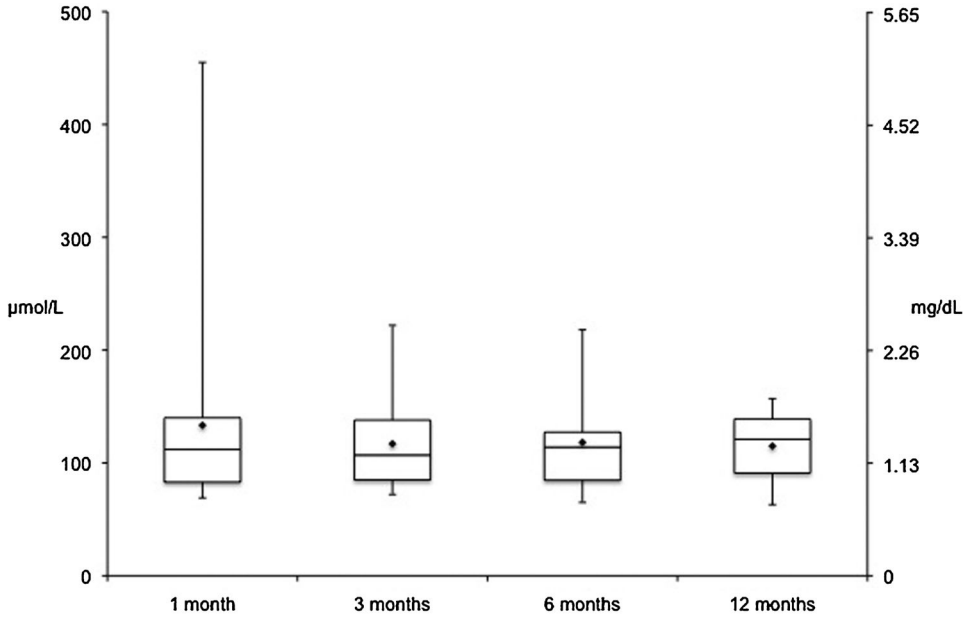

Figure 2: Kidney function at 1, 3, 6 and 12 months (serum creatinine expressed in micromoles per liter on the primary Y axis and in milligrams per deciliter on the secondary Y axis).

Four kidney recipients lost their grafts, two due to venous thrombosis (one lost both kidneys of their double transplant), one due to thrombotic microangiopathy and one due to infarction. One patient died with a functioning graft 3 months posttransplant following a cerebro-vascular event.

Liver transplantation

Eleven livers were recovered and transplanted with a median CIT of 6 h 29 min (range 2 h 49 min–7 h 30 min). The graft assessment during the NRP involved consideration of the trends of ALT and lactate during perfusion, the macroscopic aspect of the liver, the small bowel appearance, the aspect of the gallbladder mucosa and the bile duct blood flow. In four donors in Edinburgh measurements of portal and hepatic arterial flow were made during NRP with a pump flow of 2 L/min: the mean portal vein flow was 900 mL/min (range: 600–996 mL/min) and hepatic arterial flow 139 mL/min (range 80–323 mL/min).

The donor ALT changes during the NRP are illustrated in Figure 3, possibly indicating that more of the liver grafts could have been used than actually were. Of the four discarded livers where ALT changes were overlapping with utilized livers, one was turned down due to cirrhosis, one due to steatosis and one was outside current age criteria in the retrieving center (donor age 74). The remaining four grafts were discarded because of the rising ALT on a background of long WIT (1), donor history (2) and steatosis (1). The changes in lactate during NRP are illustrated in Figure 4, with no significant difference between transplanted and discarded grafts. The number of livers recovered and transplanted was higher than the current national DCD liver utilization rates (52% vs. 27%), although the use of NRP was in part related to the likelihood of liver recovery.

The demographic data for the liver transplant recipients are illustrated in Table 3. The median peak ALT during first week posttransplant was 389 IU/L (range 58–3043). The rate of ALT improvement during the first week posttransplant is illustrated in Figure 5. Four liver transplants had early allograft dysfunction as defined by Olthoff et al (14). However, only grade 1 early allograft dysfunction (as defined by first week ALT $>$ 2000 IU/L) was noted.

The mean follow-up was 10 months (range 3–36 months) with no clinical or radiological evidence of ischemic type biliary lesions by the time of reporting (minimum follow-up 3 months). One patient had an anastomotic stricture, which resolved with endoscopic retrograde cholangio-pancreatography and one patient had a bile leak on day 1 for which he underwent a Roux-en-Y conversion. One patient died of hepatitis C virus (HCV) recurrence at 8 months while awaiting re-transplantation and one patient had PNF and died. Although there were no concerns during NRP for this latter case, it was felt that the combination of a DCD graft and a complicated recipient who was found to have peritoneal sclerosis at transplant contributed to this outcome.

Islet and whole pancreas transplantation

Five pancreata were recovered from these donors. Two simultaneous pancreas–kidney transplants were performed in type I diabetic patients aged 52 and 34 years old, with primary renal and pancreatic function. The CITs for

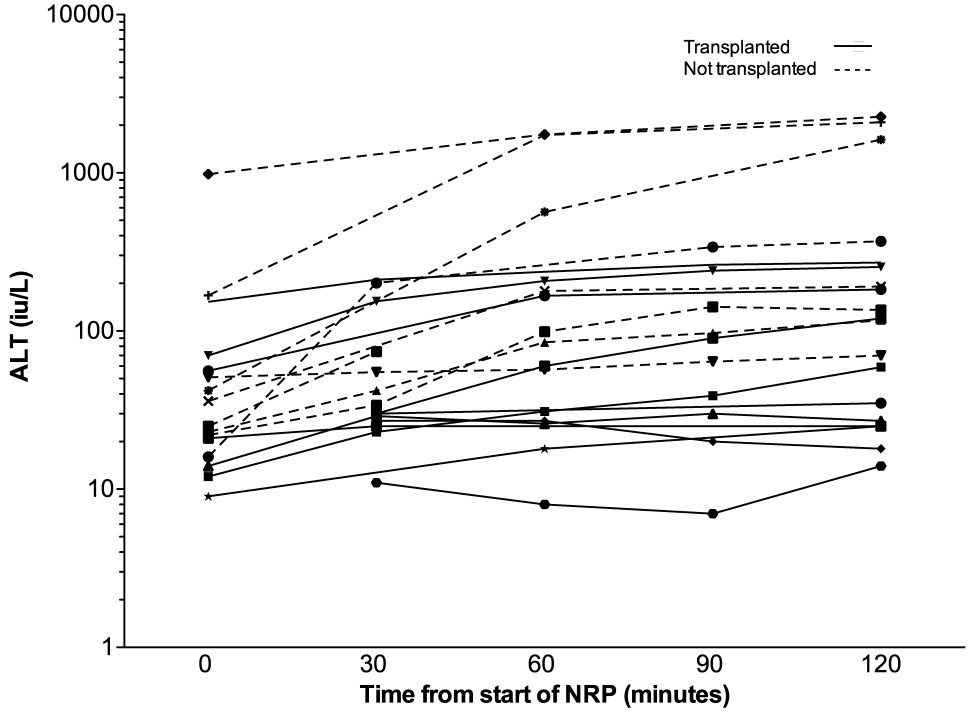

Figure 3: Changes in donor alanine transaminase (ALT) (IU/L) during normothermic regional perfusion (NRP), according to liver utilization (logarithmic scale).

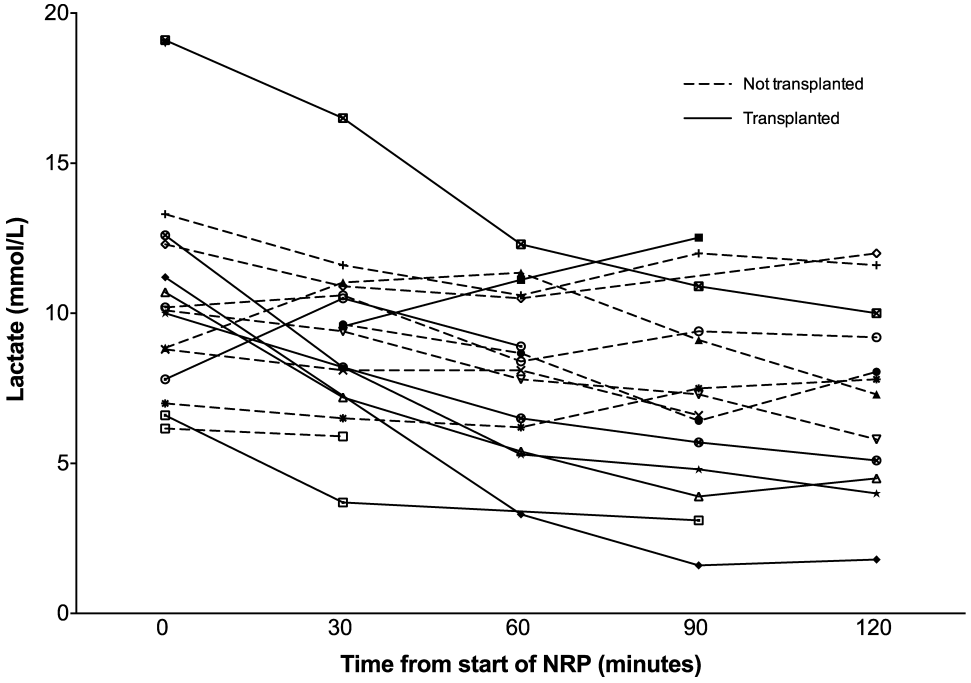

Figure 4: Changes in lactate (mmol/L) during the normothermic regional perfusion (NRP), according to liver utilization.

Table 3: Liver recipient demographic and transplant data

N = 11	Recipient data
Median age (range)	63 (43–74) years
Indication for transplant	
HCV	4
HCC + (ALD/HCV/NAFLD)	5
α1Anti-trypsin	1
Cryptogenic cirrhosis	1
Cold ischemia time–median (range)	5 h 50 min (4 h 29 min–7 h 30 min)
Anastomotic time–median (range)	33 min (22–57)
Median ITU stay–days (range)	1 (0–22)
Median hospital stay–days (range)	17 (8–42)

ALD, alcoholic liver disease; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ITU, intensive treatment unit; NAFLD, nonalcoholic fatty liver disease.

the pancreata were 8 h 52 min and 7 h 32 min, respectively. Two pancreata were sent for islet isolation. One achieved a good islet yield and was transplanted while the second one was fibrotic and achieved a lower yield than required for transplantation. The fifth pancreas was initially accepted for transplantation as a solid organ by two centers but later turned down on logistic reasons and was eventually sent for research. The remainder of the pancreata were not recovered (three citing a long WIT, eight donor age and five donor history as the reasons for nonuse).

Lung transplantation

Three double lungs were retrieved with isolated thoracic cold perfusion, and successfully transplanted as double lung transplants. This suggests that cold thoracic retrieval and normothermic abdominal perfusion can be performed simultaneously without compromising the outcome of both thoracic and abdominal organ transplants.

Discussion

In situ NRP was described in 1997 (6) and has emerged to be a useful approach to organ recovery from donors after circulatory death following the pioneering work in Spain for Maastricht category II DCD donation (uncontrolled DCD donation). In the Spanish setting of uncontrolled DCD donation, following confirmation of death, several key maneuvers are undertaken to minimize the WIT and the circulatory standstill. Mechanical cardiac compression and ventilation are re-commenced and the donor heparinized prior to cannulation of femoral vessels and balloon occlusion of the thoracic aorta. Initial reports established the feasibility of the technique and indicated an increase in organ recovery (6). The results of kidney transplantation are comparable with the results of DBD kidneys, with a reduced incidence of delayed graft function (9,16). Similarly, liver transplantation appears to be associated with a low incidence of ischemic type biliary strictures and PNF (17,18).

However, there are considerable differences between the Spanish practice of Maastricht category II donation and the more commonly practiced controlled (Maastricht category III) DCD donation (controlled donation). Therefore, the applicability of these findings remains to be further defined. A recent systematic review (19) identified five studies describing the use of regional perfusion in controlled DCD

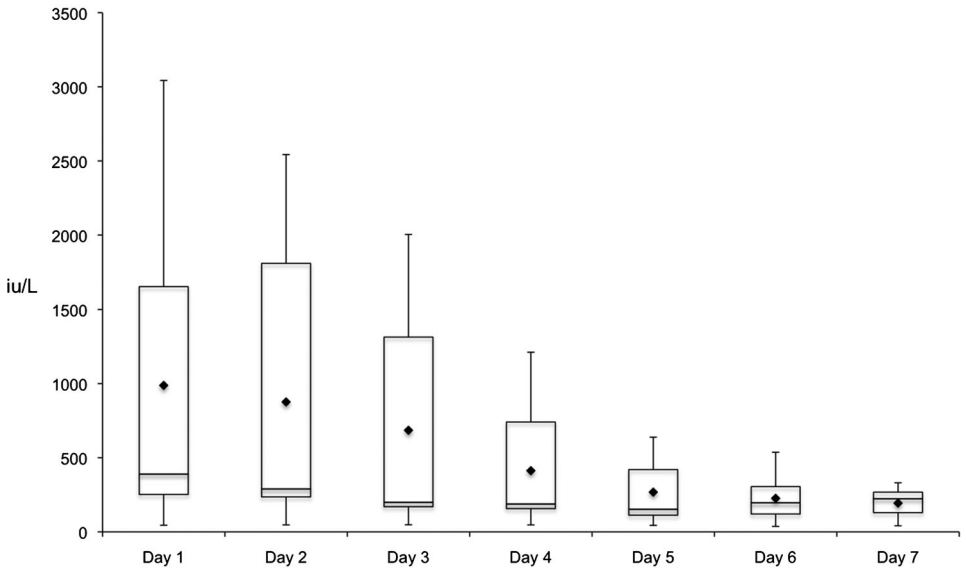

Figure 5: Changes in the alanine transaminase (IU/L) during the first week posttransplant (data shown as box and whiskers plots).

donation in normothermic (10,11) as well as hypothermic conditions (12,20). Despite the variation in the extra-corporeal temperature, these studies reported an increase in organ recovery rates compared with standard DCD donation, with a good short-term organ function. Our NRP experience is preliminary but is supported by data from a single center in the United States (10,21) that suggests it is possible to achieve similar results to those seen with DBD livers. However, the prerequisite in these studies was the ability to administer heparin and perform vascular cannulation prior to patients' death, which theoretically reduces the risk of thrombosis and may improve perfusion of the organs *in situ*, with fewer posttransplant complications.

Our study investigated the feasibility of NRP in category III DCD donation within the setting of a national organ retrieval service with national sharing of livers, kidneys and pancreata. The key difference between the studies reported previously and the UK practice is that premortem vascular cannulation and heparin administration are prohibited. Furthermore, withdrawal of therapy often takes place in intensive care units and therefore, there is a prolonged asystolic period, which includes the 5 min mandatory observation period prior to verification of death, followed by the time taken to transfer to the operating room. This minimizes the number of potential donors that could yield extra-renal organs, due to the stringent warm ischemic criteria described (although NRP may lead to revision of these criteria). There is also concern that hypo-perfusion during the agonal phase and following circulatory arrest could lead to clot formation both *in situ* and in the circuit that may prevent establishing the extra-corporeal circulation.

We have shown that, in spite of the lack of premortem interventions, it is possible to establish NRP successfully and continue normothermic perfusion for a period of 2 h. The use of shunts to bypass the oxygenator (and reservoir, where applicable), was empirical to avoid intra-circuit thrombus but may in fact not be necessary. Further work is necessary to determine this. In addition, although microthrombi were not seen on implantation biopsies of the kidneys, there may be a place for a thrombolytic in the initial perfusate, or for different approaches to systemic heparin delivery (22) if they were believed to be a risk.

The optimal duration of NRP is yet to be fully determined. Although in the uncontrolled donation setting is Spain, NRP is maintained for up to 4 h, this may not be required and in fact may be logistically difficult in the setting of controlled DCD donation in smaller referring hospitals. Furthermore, recent data appear to suggest that even a shorter NRP duration may reverse the ischemic damage and provide a good outcome (21).

Significantly fewer organs are recovered from DCD donors compared with DBD donors (1,2) due to the period of warm ischemia. A period of normothermic perfusion could potentially reverse these effects, by restoring the supply of oxygen to the tissues during retrieval, and improving the organs' tolerance to a subsequent period of cold storage with a resultant increase in organ recovery and utilization. In this study, we achieved an excellent organ recovery and transplant rate, with good post-transplant function, despite maintaining the same selection criteria for donor and organ utilization. One benefit of NRP may be to expand organ utilization criteria, as well as increasing the potential organ recovery from current criteria DCD donors. In the United Kingdom, only 27% of the livers recovered from DCD donors are transplanted compared to 83% from DBD donors. Similarly, only 8% of the DCD pancreata are transplanted compared with 28% in the DBD setting (1).

Transplantation of organs from DCD donors is fraught with significantly higher rates of complications and transplant failure. This study achieved beneficial short- and medium-term outcomes. The delayed graft function rate in kidney transplantation is lower than that currently seen in the United Kingdom, while the function within the first 12 months is encouraging. It can be argued that this is a small cohort, but given that the donor selection criteria and organ allocation for DCD were not altered for the purpose of this study, the kidney function noted is encouraging and warrants a larger scale investigation. Three kidney recipients lost their grafts due to venous thrombosis. The rate of venous thrombosis is higher than expected and although no direct correlation with the normothermic perfusion was established, further monitoring is warranted to ensure that this is not related.

Although the liver transplant experience is limited and the follow-up is relatively short, it was reassuring to see that no patient developed ischemic type biliary strictures. Furthermore, the rate of improvement in ALT in the first week (as a marker of ischemia-reperfusion injury) appeared to be quicker, although this needs further evaluation given that the number of NRP cases is small. The one liver recipient who died from PNF is a concern. There was no obvious donor parameter (young age, short functional WIT) or perfusion characteristic (improving lactate and ALT trends), which suggested a suboptimal graft. However, the complex recipient (encapsulating peritoneal sclerosis) and difficult implantation may have contributed to this graft failure.

Organ procurement from DCD donors is associated with a higher rate of organ injury and discard, most likely due to the haste in removing the organs to minimize the WIT (23). The use of NRP is likely to reduce the rate of damage, as it re-establishes the abdominal circulation, allowing a careful identification of the vascular structures and enables the procedure to be performed without undue speed, compared to traditional DCD organ recovery. Although no mechanistic investigations were performed during this feasibility study, there are some indications, from a small cohort in Cambridge, that NRP restores adenosine triphosphate (24). Furthermore, we noted that there is a significant drop in the white cell count within the first hour of NRP (data

not shown), which may represent leukocytes adhering to endothelium in response to the initial warm ischemia. As such, the incorporation of a leukocyte filter into the perfusion circuit warrants further investigation.

DCD lung transplantation is associated with good outcomes (25). In the setting of normothermic abdominal perfusion, the thoracic organs were removed first using cold perfusion, while continuing the NRP, albeit with some additional blood loss in two cases. As a consequence, the thoracic procurement protocol required modifications to allow the lung recovery to take place with standard cold perfusion and maintain hemostasis and allow the NRP to be carried on for the desired duration.

Increasingly, normothermic perfusion appears to be a better alternative to cold perfusion and storage. Early reports suggest that a period of *ex situ* normothermic machine perfusion for livers (26) and kidneys (27) is feasible and allows organ function assessment, therapeutic interventions and reconditioning as well as expansion of acceptance criteria. The clinical experience with normothermic perfusion techniques (both *in situ* and *ex situ*) is in its infancy and their place in the organ recovery and preservation pathway is yet to be fully established. There are suggestions that continuous normothermic perfusion, combining a period of *in situ* NRP in the donor followed by *ex situ* normothermic perfusion may provide the best outcome (28). This needs to be explored further in the setting of a randomized controlled clinical trial.

The results of this study are encouraging on many accounts such as organ function and recovery rate. While NRP will not change organ allocation it may lead to a wider utilization and sharing of organs currently discarded or indeed lead to more liberal acceptance criteria. Beyond the United Kingdom, these results may encourage an increase in DCD organ utilization in other countries where such programs have been slow to develop due to logistics or concerns regarding outcome. The results need to be replicated in larger (randomized) studies to define the true benefit of NRP, the cost implications of the technology and the potential to expand organ acceptance criteria. The NRP parameters that could categorically inform the organ selection criteria (especially for the extra-renal organs) are yet to be defined.

In conclusion, *in situ* NRP represents a significant advance in DCD organ retrieval and has the potential to increase the number and quality of the transplanted organs. Further studies are required to fully assess the impact on organ recovery rates and to quantify the extent of ischemic injury modulation.

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Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

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