Liver transplantation after normothermic regional perfusion from controlled donors after circulatory death: The Norwegian experience.

Authors: Morten Hagness,[1] Stein Foss[1], Dag Wendelbo Sørensen [2], Torgunn Syversen [2], Per Arne Bakkan [1], Thorleif Dahl [3], Arnt Fiane [3], Pål-Dag Line[1]

[1]Section for Transplantation Surgery, Division for Surgery and Transplantation, [2] Department of Intensive Care Medicine, Division of Emergencies and Critical Care, [3]Department of Cardiothoracic Surgery, Oslo University Hospital, Oslo, Norway.

E-mail adresses: Hagness: mhagness@ous-hf.no; Foss: sfoss@ous-hf.no; Sørensen: UXDAWS@ous-hf.no; Syversen: UXTOSY@ous-hf.no; Bakkan: pbakkan@ous-hf.no; Dahl: thorda@ous-hf.no; Fiane: afiane@ous-hf.no; Line: pline@ous-hf.no

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Corresponding author:

Morten Hagness, MD, PhD, FEBS

Oslo University Hospital

Postboks 4950 Nydalen

0424 OSLO, Norway

Phone: +47 23 07 05 00 /Fax + 47 23 07 05 10

E-mail: mhagness@ous-hf.no

Abstract:

Background:

In order to meet the increasing demand for donor organs the concept of donation after circulatory death (DCD) was reintroduced in Norway. First a pilot study, followed by the use of DCD as an institutional practice. We here report the current Norwegian experience with liver transplantation following DCD.

Methods:

After acceptance from next of kin, life support was withdrawn and cardiac arrest observed. After a five minute "no-touch" period, extracorporeal membrane oxygenation for post mortem normothermic perfusion (NRP) by ECMO circuit was established. Data from all liver transplant recipients receiving cDCD livers in Oslo were analyzed.

Results:

From 2015 to 2017, 8 patients underwent liver transplantation with cDCD and NRP livergrafts in Norway. Median MELD was 26, (range 6-40). There were no cases of delayed graft function or graft loss. Seven patients have reached 1 year of follow- up, 1 patient has reached 6 months. Two patients have recurrence of primary disease (PSC and steatohepatitis). All patients had normalized liver function at last follow-up.

Two patients underwent procedures for the biliary complications: One with leakage from the cystic duct which was successfully handled endoscopically by stenting. In the other patient, a suspected stricture on MRI led to an ERCP procedure which did not confirm signs of biliary stenosis. There was one instance of hepatic artery stenosis, which was managed with endovascular technique.

Conclusion:

The results after liver transplantation using cDCD with NRP are good. The rate of complications seems to be within the same range as when using conventional DBD grafts

Background:

In order to meet the increasing demand for donor organs, the concept of donation after circulatory death (DCD) was reintroduced in Norway in 2009. First, a pilot study comprising 8 donors were performed until 2015, followed by the use of DCD as an institutional practice at Oslo University Hospital. A total of 18 DCDs were procured until November 2017, when the program was temporarily stalled in order to evaluate the method at a national level. In Europe, the DCD represents a valuable source of liver grafts in an expanding number of countries, accounting for 27% of liver donors in Netherlands, and 18% in United Kingdom. [1] In the Norwegian study and subsequent practice, controlled DCD (cDCD) with the use of normothermic regional perfusion (NRP) was chosen as technique. There are several reasons for this. It allows the end-of-life care to be performed with minimal deviation within the ICU, and with health care staff familiar with the next of kin. Furthermore, the NRP procedure can be done efficiently and the donor transferred to the operating room with minimal urgency in contrast to the more widely used rapid organ recovery technique by laparotomy or double balloon catheter.[2] Also, cDCD has been hampered with complications such as ischemic cholangiopathy, primary non-function and arterial thrombosis for in liver recipients, and primary non function in kidney patients. These complications are associated with the prolonged warm ischemia time (CIT) inherently connected with the cDCD procedure. Utilizing NRP by means of extracorporeal membrane oxygenator (ECMO) has the potential of improving the quality of DCD organs by avoiding prolonged warm ischemia and possibly reversing ischemic damage.
We here report the outcome of the first 8 liver transplantations performed with cDCD and NRP in Norway.

Methods:

The first two patients in the cohort were included in a single center pilot study, while the remaining 6 was performed within the subsequent institutional protocol for controlled DCD at Oslo University Hospital. The background and approach for the single-center pilot study is given in detail elsewhere. [2] Briefly, this was a study approved by the Norwegian regional committee for medical and health research ethics and given institutional support by Oslo University Hospital. Inclusion criteria were patients aged 16 to 60 years in a coma with documented devastating brain injury, and on mechanical ventilation that on the basis of clinical assessment were most likely to attain cardiac arrest within 60 minutes after extubation. Potential cDCD donors were recruited in cases where the next of kin already had accepted withdrawal of life sustaining treatment (WLST) and where the donor criteria for brain death where unlikely to be met. The potential donors were referred to the national organ procurement organization for evaluation. The families were approached regarding possible DCD donation if the potential donors were considered to be medically suitable. After consent for donation was granted, the NRP team was notified. Premortem patient management was conducted by the ICU team not affiliated with the organ donation service. The cDCD protocol used NRP support of abdominal organs by an ECMO circuit. After permission was granted, central lines were placed in the common femoral artery and vein. 5000 international units Heparin® was given intravenously at WLST. Preparations for abdominal NRP were performed bedside in the ICU but without cannulation for perfusion before declaration of death. After a minute of silence, life-support was withdrawn and symptomatic directed measures continued as needed. The patients were extubated and intravenous support and vasoactive medications were stopped. Upon wish, the next of kin could be present bedside during the agonal period. After cardiac and respiratory arrest, and a 5-minute observation constituting a “no-touch period,” the primary responsible intensive care physician made the declaration of death. The next of kin left the room after the observation period. Using Seldinger percutaneous technique, cannulas were rapidly placed for the NRP circuit thereby providing an organ preservation flush line. To avoid cardiac reanimation and cerebral reperfusion, the thoracic aorta was occluded with a double-lumen 7-Fr inflated balloon catheter which in addition allowed pressure measurements above the balloon to verify total occlusion of aorta when perfusion was initiated. Perfusion fluid was University of Wisconsin for the two first donors, IgL for the remaining 6 donors. A strategy to confirm correct balloon catheter

placement by radiopaque contrast was introduced during the study period. Functional warm ischemic time (fWIT) for organs was defined as the time from mean blood pressure (BP) less than 50 mm Hg and/or oxygen saturation less than 80% (5 minute of "no-touch period" included) to NRP start. Organs were accepted for transplantation according to EDQM guidelines[19] with a maximum fWIT 30 minutes for livers. For the 6 remaining donors the donation process followed the Norwegian protocol for cDCD. The upper limit of donor age was altered to 70 years; the remaining procedure was identical to the study protocol. Functional warm ischemic time (fWIT) was defined as time from when mean blood pressure was below 50 mmHG in more than 2 minutes to start of NRP.

Potential liver cDCD patients were recruited from 2009 to 2015 after obtaining written informed consent accepting to receive a cDCD organ. After end of study, the cDCD livers were allocated to patients at the discretion of the Department of Transplantation Medicine at Oslo University Hospital. Data from all liver transplant recipients receiving cDCD livers and the corresponding cDCD donors in the period of 2009-2017 Oslo were analyzed. The immunosuppression regimen involved basiliximab, mycophenolate mofetil, steroids and tacrolimus.

Results:

cDCD donors

From November 2015 to November 2017, 8 donors procured by cDCD with NRP were utilized for liver transplantation after next-of- kin consent to donation. Median age was 49,5years (23-63 years); two donors were older than 60 years. Median BMI was 26.5 kg/m^2. The causes of death was one subarachnoidal hemorrhage, three traumatic brain injuries, three cases of anoxia and one donor had cardiac arrest while the patient was on ECMO. All donors were accepted and utilized for two kidney transplantations each; one was accepted for islet transplantation. At time of organ donation the median alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were 80, 5 U/L (13-279 U/L) and 93, 5 U/L (34-401 U/L) respectively, median INR was 1, 2 (1-1, 4). Cardiac arrest occurred after a

median of 12 minutes (10-83 minutes), no episodes of auto-resuscitation were observed. The median fWIT was 28 minutes (13-24 minutes) and median NRP time was 94 minutes (73-221 minutes). All donors required SAG transfusion to keep hemoglobin over 8 g/dL, median 2 units (1-3 units). During NRP there was a median drop in lactate of 4,5 mmol/L (0,4-9,4 mml/L). Background of donors and procedural characteristics are given in Table 1

Liver recipients:

There were 8 recipients with median age 59 years (35-68 years). The indications for liver transplantation were:1) Steatohepatitis, 2) Hepatitis C virus cirrhosis, 3) PSC, 4) Post resection liver failure after resection for HCC, 5) Re-transplantation after graft failure of an ABO incompatible graft in an acute on chronic patient,6) Non-resectable colorectal metastases, 7) NASH with HCC and 8) cryptogenic cirrhosis, possibly autoimmune hepatitis. CIT was median 7, 14 hours (3, 43-9, 55 hours). One choledocho-duodenostomy were performed, one choledocho-jejunostomy and the rest were choledochal duct to duct anastomoses without the use of T-tubes. All transplantations were performed as piggyback procedures. Three of the patients were in the intensive care unit with MELD scores of 33, 40 and 40 respectively and suffered from multi organ failure pre-transplantation.

Outcome:

There were no cases of delayed graft function or graft loss. ALT levels were maximum median 991 U/L (290- 3533 U/L) after liver transplantation and at three weeks postoperatively the median level was 51 U/L (15-86 U/L). Seven patients have reached 1 year of follow- up, 1 patient has reached 6 months. Two patients have recurrence of primary disease (PSC and steatohepatitis) at one year follow-up. All patients had normalized liver function at last follow-up.

Two patients underwent procedures for biliary complications: One with leakage from the cystic duct which was successfully handled endoscopically by stenting. In the other patient, a suspected stricture at the level of anastomosis on MRI led to an ERCP procedure 7 months post transplantation. However, this did not confirm signs of biliary stenosis; a stent was placed with no effect on liver function. There

was one instance of hepatic artery stenosis at from the level of anastomosis and 20 mm distally, which was managed by endovascular technique two months postoperatively. Two patients were re-operated several times for wound-closure and wound infection. All complications with Clavien- Dindo score of more than IIIB, requiring surgical and endovascular intervention occurred in two patients with high MELD score. One in a patient who underwent rescue liver transplantation for hepatic failure post liver resection; this patient had a MELD score of 40 and underwent a myocardial infarction prior to liver transplantation, and had developed portal vein thrombosis. The operation was challenging, with 30 units of SAG given. This patient was reoperated several times for wound closure, and was endoscopically treated for a leakage from the cystic duct, (Clavien Dindo IIIb). The other patient was a rescue liver transplantation 5 weeks after an ABO incompatible liver transplantation for acute on chronic liver failure. This patient had kidney failure and on dialysis with MELD score of 33, the patient underwent several operations for wound closure and experienced hepatic artery stenosis, the patient was in need of dialysis for the first weeks postoperatively and had still kidney failure at one year follow up. (Clavien Dindo IV). [3]

Conclusion:

The introduction of the cDCD with NRP in Oslo in 2015 to 2017 yielded 8 donor livers with good long term performance and acceptable complication rate.

The uses of cDCD donors for liver transplantation have been associated with several complications. Especially, the incidence of ischemic cholangiopathy has been reported to be high but also increased levels of primary nonfunction, arterial thrombosis and acute kidney injuries have been reported. [4-6] The main reason for this is attributed to the warm ischemia time and subsequent organ preservation injury. The use of NPR in this setting provides means to minimize the ischemic injury by restoring circulation with oxygenated blood in situ. In the largest series to date, no cases of ischemic cholangiopathy and no graft loss was observed in 46 patients in a single center observational study on

liver transplantation on cDCD using NPR at Cruces University Hospital, Spain. [7] The main difference between that series and the current is that Spanish law allows for pre mortem cannulation which results in even shorter warm ischemia. They report a median WIT of 10 minutes (6-22 minutes) defined from systolic blood pressure less than 60 mmHg to establishment of NRP perfusion. Although, the fWIT in this report is considerably longer, 28 minutes (13-24 minutes), the results in current series seems to be in line with the Spanish results. In our experience no cases of cholangiopathy, defined as nonanastomotic biliary stricture without a concomitant hepatic artery thrombosis, was recorded, further there were no cases of graft loss.

Two of the donors were more than 60 years old; both liver transplantations were performed without complications. The oldest donor liver was 63 years old, and was given to an intubated ICU patient, age 61 with MELD score of 40. The observational time for this liver is only 6 months, but so far the graft function is excellent and there are no complications. It is noteworthy that three of the patients were intensive care patients with MELD of 33-40 and multi organ failure. The reason for using cDCD livers in this setting were high degree of urgency and lack of DBD organs in all three cases. All three patients have good liver function at last follow up; one has continuously a light degree of kidney failure not requiring dialysis. However, two of these patients experienced the most serious complications (Clavien Dindo IIIB and IV). Nonetheless, the sample size of this report is too limited to draw conclusions from this finding.

The results after liver transplantation using cDCD with NRP livers are excellent and have the potential to contribute to the donor pool with high quality donor organs. The rate of complications seems to be within the same range as when using conventional DBD grafts. Reimplementation of cDCD with NRP would provide a valuable source of donor livers in Norway.

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Table 1 Donors and procedural characteristics:	
Age, y	49,5 (23-63)
Male sex, n (%)	5 (63)
BMI, kg/m^2	26,5 (17-29)
Cause of death	
- CVA	1
- Anoxia	3
- TBI	3
- Others	1
ALT at time of OD, (U/L)	80,5 (13-279)
Days ICU	5 (2-19)
Aystole, min	11,5 (10-83)
fWIT minutes	28 (13-24)
WIT minutes	29 (16-96)
Total NRP time (start-stop), min	94 (73-221)
NRP Surgical procedure, min	9 (0,5-16)
Drop in lactate, mml/L	4,5 (0,4-9,4)

Values are median (range).

CVA- cerebrovascular accident, TBI - traumatic brain injury, fWIT – functional warm ischemic time, (time for mean blood pressure below 50 mmHG in more than 2 minutes to start of NRP) , WIT – warm ischemia time, CIT- cold ischemic time, NRP – normothermic regional perfusion. ALT - Alanine Aminotransferease

Table 2 Liver recipients	cDCD (n=8)
Age, years	59 (35-68)
Male sex, n (%)	75%
MELD score	26(6-40)

CIT hours	7,14 (3,43-9, 55)
DGF, n (%)	0 (0%)
Graft loss, n(%)	0 (0%)
Maximum ALAT after Ltx (U/L) :	991 (290- 3533)
ALAT at 3 weeks post Ltx (U/L):	51(15-86)
Allograft rejections n	1

Values are Median (range) unless otherwise specified

cDCD; controlled donation after circulatory death, DGF; delayed graft function,