First Scandinavian Protocol for Controlled Donation After Circulatory Death Using Normothermic Regional Perfusion

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Background. Donation after circulatory death (DCD) can increase the pool of available organs for transplantation. This pilot study evaluates the implementation of a controlled DCD (cDCD) protocol using normothermic regional perfusion in Norway.

Methods. Patients aged 16 to 60 years that are in coma with documented devastating brain injury in need of mechanical ventilation, who would most likely attain cardiac arrest within 60 minutes after extubation, were eligible. With the acceptance from the next of kin and their wish for organ donation, life support was withdrawn and cardiac arrest observed. After a 5-minute no-touch period, extracorporeal membrane oxygenation for post mortem regional normothermic regional perfusion was established. Cerebral and cardiac reperfusion was prevented by an aortic occlusion catheter. Measured glomerular filtration rates 1 year posttransplantation were compared between cDCD grafts and age-matched grafts donated after brain death (DBD). Results. Eight cDCD were performed from 2014 to 2015. Circulation ceased median 12 minutes after withdrawal of life-sustaining treatment. Fourteen kidneys and 2 livers were retrieved and subsequently transplanted. Functional warm ischemic time was 26 (20-51) minutes. Regional perfusion was applied for 97 minutes (54-106 minutes). Measured glomerular filtration rate 1 year posttransplantation was not significantly different between cDCD and donation after brain death organs, 75 (65-76) mL/min per 1.73 m² vs 60 (37-112) mL/min per 1.73 m² (P = 0.23). No complications have been observed in the 2 cDCD livers. Conclusion. A protocol for cDCD is successfully established in Norway. Excellent transplant outcomes have encouraged us to continue this work addressing the shortage of organs for transplantation.

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Organ transplantation is a successful treatment for most end-stage organ failures, but patients die on the waiting list due to organ shortage. Oslo University Hospital is the only transplant center in Norway, but also 1 of 26 Norwegian donor hospitals. During the last 5 years, an increase in national waiting time for transplantation has been observed, especially for kidney transplantations due to declining donation after brain death (DBD) rates from 25.6 per million population (PMP) in 2011 to 20.2 PMP in 2016.1 A fair number of patients with devastating brain injury do not develop cerebral tamponade with intracranial circulatory arrest. According to Norwegian law, patients who die should, if possible, be provided with the opportunity to donate.2 Without a functioning nationwide donation after circulatory death (DCD) program, some patients lose this possibility. The World Health Organization has encouraged all societies to develop responsible policies concerning donation after death and the adoption of DCD worldwide.3 The introduction of a program for DCD has the potential to increase the donor pool and thereby provide the possibility for organ transplantation to more eligible patients and reduce

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waiting lists. Successful DCD programs are already established in Spain, United Kingdom, Belgium and in The Netherlands with 7.8 to 10.7 DCD donors PMP in 2016. Additionally, USA, Australia, Latvia, and France have well-developed DCD programs with 1.4 to 5.5 DCD donors PMP. A higher incidence of delayed graft function (DGF) among DCD kidney recipients has been reported compared with DBD recipients, and inferior results with DCD liver transplantation have been associated with warm ischemic injury. 4,5 Currently, the majority of European centers performing controlled DCD (cDCD) defined as Maastricht class III use a rapid organ recovery technique by laparotomy or by double balloon catheter. 8 Using abdominal normothermic regional perfusion (NRP) by means of extracorporeal membrane oxygenator (ECMO) may improve the quality of DCD organs and reduce the incidence of DGF by avoiding prolonged warm ischemia and possibly reversing ischemic damage. 9-15 The ETHICUS study showed that withdrawal of life sustaining treatment (WLST) on the basis of futility is frequently done in intensive care units (ICU) and are more applied in northern than southern European countries. 16 Forty-five to 50 years ago, in the early era of transplantation, cDCD was used in Norway to provide organs for kidney transplantation, 17 but this practice ended when the transplantation law was implemented in 1973. 18 The objective of this pilot study is to evaluate the clinical results of the first cDCD protocol in Scandinavia using NRP.

MATERIALS AND METHODS

A single-center pilot study was approved by the Norwegian regional committee for medical and health research ethics (1.2008.832) and given institutional support by Oslo University Hospital. Inclusion criteria for protocol eligibility 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 WLST and where the donor criteria for brain death were 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 (Figure 1) when perfusion was initiated. 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...
Donor characteristics

|                      | cDCD (n = 8) | DBD (n = 114) | P     |
|----------------------|--------------|---------------|-------|
| Age, y               | 50.3 (34-60) | 46.0 (16-60)  | 0.15  |
| Male sex, n (%)      | 8 (100%)     | 69 (61%)      | 0.02  |
| BMI, kg/m²           | 26.9 (22.2-35.1) | 24.7 (14.3-48.6) | 0.32  |
| Creatinine, mmol     | 72.0 (36.0-81.0) | 69.0 (29-469)  | 0.53  |
| Cause of death       |              |               |       |
| CVA, n (%)           | 2 (25)       | 41 (36)       | 0.71  |
| Anoxia, n (%)        | 3 (37.5)     | 16 (14)       | 0.10  |
| TBI, n (%)           | 3 (37.5)     | 24 (21)       | 0.39  |
| Others, n (%)        | 0            | 33 (29)       | 0.11  |
| Days in ICU          | 4 (2-18)     | 2 (0-30)      | 0.15  |
| Asystole, min        | 12 (6-24)    |               |       |
| fWIT min             | 26.5 (20-49) |               |       |
| NRP surgical procedure, min | 10.5 (8-34) |               |       |
| Total NRP (start-stop), min | 97 (54-106) |               |       |
| Drop in lactate during NRP, mmol/L | 5 (2.2-7.7) |               |       |

Values are median (range) unless otherwise specified.

BMI, body mass index; CVA, cerebrovascular accident; TBI, traumatic brain injury.

RESULTS

cDCD Donors

During 2014 and 2015, 8 male donors were eligible and included in the study after next-of-kin consent to donation. Median donor age was 50 years and median body mass index 27 kg/m². Cardiac arrest occurred after a median of 12 minutes (6-24 minutes), and no episodes of autoresuscitation were observed. Seven donors were cannulated using Seldinger technique, while 1, due to difficult vascular access, was converted to a cut-down procedure. The median fWIT was 26 minutes (20-51 minutes). Median NRP time at 37°C was 97 minutes (54-106 minutes) with median circuit flow of 3.0 L/min (1.7-4.0 L/min). All but 1 patient required SAG transfusion to keep hemoglobin levels above 8 g/dL; with a median of 2 unites (0-5 units). No severe bleeding was observed. During NRP, the pH values normalized, the venous saturation kept above 60% and the active clotting times kept above 350 seconds. In all but 1 case, a substantial drop in lactate values during NRP was observed with a median of 5.0 (2.2-7.7) mmol/L. One donor had the aortic occlusion catheter misplaced at the level of the left renal artery, resulting in increased lactate values from 10.4 to 17.0 mmol/L during NRP. These ischemic organs could not be used for transplantation. Fourteen kidneys and 2 livers were retrieved and subsequently transplanted from cDCD donors. As the pilot study was designed to retrieve kidneys and livers, only a mean of 2.3 organs from each cDCD donor were transplanted. In simultaneously performed DBDs, the number was 4.4 (including heart, lungs, and pancreas). As shown in Table 1, there were no significant differences regarding the characteristics between cDCD and age-matched DBD donors.

cDCD Kidneys

The characteristics of the cDCD kidney recipients and clinical outcomes are presented in Table 2. One DCD recipient had DGF and lost the graft due to chronic rejection 4 months after transplantation. Cold ischemia time (CIT) for cDCD kidneys were significantly lower than that in the DBD control group.

There were no significant differences in measured glomerular filtration rate between cDCD and DBD kidney recipients at 8 weeks and 1 year after transplantation; 66 vs 59 mL/min

Kidney recipients' characteristics and outcomes

|                      | cDCD (n = 14) | DBD (n = 163) | P     |
|----------------------|--------------|---------------|-------|
| Age, y               | 58 (34 71)   | 52 (2-80)     | 0.22  |
| Male sex, n (%)      | 10 (71.4%)   | 111 (68%)     | 0.79  |
| CIT, min             | 360 (174-624)| 767 (233-1688)| <0.005|
| DGF, n (%)           | 1 (7.1%)     | 8 (4.9%)      | 0.53  |
| Iohexol GFR week 8 posttransplant (mL/min per 1.73 m²) | 665 (51-78) | 59 (31-106)  | 0.19  |
| Iohexol GFR week 52 posttransplant (mL/min per 1.73 m²) | 75 (65-76)   | 61 (37-112)   | 0.23  |
| Graft loss at 12 mo, n (%) | 1 (7.1%)   | 8 (4.9%)      | 0.53  |

Values are median (range) unless otherwise specified.

DGT, delayed graft function.
per 1.73 m² at 8 weeks and 75 vs 61 mL/min/1.73 m² at 1 year posttransplant, respectively. The 1-year graft survival of cDCD and DBD group was 93% and 95%, respectively.

**DCD Livers**

Two of 5 livers accepted for transplantation were transplanted. The fWIT was 23 and 26 minutes, the CIT was 225 and 428 minutes, respectively. Both liver grafts had primary function, and at 2 years posttransplant, both recipients had normal liver function tests without signs of biliary complications.

**DISCUSSION**

We have reintroduced and refined a previously used method that provides an opportunity to pursue organ donation as end-of-life care, an option otherwise not used in Norway for decades. The initial clinical results of the new protocol are in line with other reports and support the postulation that NRP seems favorable in a cDCD setting.9–15

After the first cDCD in April 2014, the remaining 7 donations were done within 1 and a half years. The pilot study was originally accepted by the Regional Ethical Committee and started in December 2009. From 2009 to 2014, several patients were initially evaluated but were found to be ineligible due to social, cultural, or language difficulties. Besides, we experienced resistance toward cDCD within and between different medical, ethical, and legal professions. The concept is now under scrutiny and being evaluated by a governmental-appointed official body before a national implementation may take place.

There were several reasons for choosing NRP as retrieval technique. Normothermic regional perfusion allows end-of-life care to be performed with minimal deviation, within the ICU, bedside, and by healthcare staff familiar to the next of kin. Furthermore, the NRP procedure can be done efficiently and the donor transferred to the operating room with minimal urgency. Consequently, in contrast to a rapid recovery technique, the NRP procedure offers the next of kin the possibility to bid a last farewell before leaving the ICU. We have previously published results on the importance of careful planning, good practices, and attention to individual needs for both the patients and their families.20 Our results found that bereaved families of cDCD donors where NRP are used to demonstrate an overall positive experience during the different phases of the donation process.20

Additionally, compared with a rapid removal technique, NRP provides a controlled environment and reanimation of ischemic organs, also allowing careful visual inspection and excellent quality control, helping to avoid iatrogenic damage to organs and may also reduce the risk of staff injury during surgery. After abdominal inspection, NRP, during retrieval, allows the transplant teams to start the recipient operation and thereby minimize CIT. As the importance of keeping CIT short especially for kidneys with long WIT/fWIT has been documented21 we focused on keeping the CIT as low as possible for the cDCD organs. Median CIT for cDCD kidneys ended up significantly lower than that in the DBD control group which may have contributed to our low reported DGF rate after cDCD.

Like most cDCD programs, our protocol includes a 5-minute observation “no-touch period” after asystole to ensure permanent cessation of circulation.8 In line with the experience of others,22 we did not encounter any signs of autoresuscitation after asystole.

In the United Kingdom, nearly 40% of cDCD donations are aborted after treatment withdrawal, usually because the time limit is exceeded.23 In our series, all patients went into cardiac arrest within the 60-minute stand down time. Evaluation tools with scoring systems have been developed in an attempt to predict the time of progression to cardiorespiratory arrest.24,25 These tools are yet to be validated prospectively and remain of uncertain benefit. They do not take into account the use of pharmacological symptomatic care with analgesics and/or sedatives after life support withdrawal.23,26–27 For these reasons, we decided not to use any scoring system, but relied on the clinical judgment by the intensive care physician. We restrictively selected potential donors only implementing those most likely to proceed to asystole within 60 minutes. However, in the future, when a broader range of cDCD candidates are accepted as donors, we must expect that donations could be aborted due to exceeding stand down time limits. Our new protocol has a 90-minute limit, but due to the good results in the United Kingdom,5,28 showing little effect on prolonged stand down time and without using NRP, we will consider expanding to 120 minutes.

We experienced 1 misplacement of the aortic balloon catheter, consequently, no organs from this donor were used. This incident taught us to follow lactate values carefully and to verify the aortic balloon position by radiologic imaging.

The cutoff limits for accepting organs for transplantation was based on fWIT, using the definition of a drop to mean BP less than 50 mm Hg and/or oxygen saturation less than 80%. After the pilot study was carried out, the more common definition of fWIT (mean BP, <50 mm Hg for a longer period than 2 minutes) has been used.29 If we apply this definition on our data set, the median fWIT would have been 18 minutes (15–40 minutes) versus 27 minutes (20–51 minutes).

The numbers of used organs per donor were lower in the cDCD group (mean, 2.3 organs) compared with the DBD control group (mean, 4.4 organs). The difference is in line with previous experiences from similar protocols8–9,30 and is partly due to the fact that the lungs and pancreas were not used according to our protocol. However, the difference indicates that the lower yield of transplantable grafts could be expected during the learning curve. We acknowledge the fact that lungs and pancreas were retrieved and successfully transplanted in centers with similar NRP protocols.9

Prolonged warm ischemia is particularly harmful for liver grafts where increased incidence of ischemic cholangiopathy has been reported.7 Recent publications have shown favorable posttransplant results using NRP to improve organ quality after ischemic damage.9,15 We had hoped to gain more experience from liver transplantation after NRP, but disappointingly, in 3 cDCD cases, the livers were not used because there were no blood group-compatible patients on the expanded waiting list. The pretransplant written information to recipients indicated a slightly lower expected result in comparison to DBD which may have affected the recruitment of cDCD liver recipient candidates. Our good experiences with the 2 liver transplants performed are encouraging, but does not justify any conclusions.

Prolonged CIT and DGF have previously shown little impact on long term cDCD kidney graft survival.5,28
current protocol resulted in few DGF numbers compared with results from cDCD without NRP, showing results comparable to those obtained with DBD donation. However, the DGF observed might be due to the short CIT compared with other experiences. In a paired kidney analysis, Lim et al. have challenged the previously held belief that DGF has no deleterious effect on graft outcome. They showed that 3-year death-censored graft survival for DCD recipients was 14% lower in the absence of DGF compared with those who did experience DGF. Normothermic regional perfusion and low CIT might be an effective method to minimize the detrimental effects of warm ischemia during DCD donation and potentially improve graft survival.

Our study has shown that NRP allows a comprehensive assessment of organ viability, converts a stressful rush during retrieval, and provides valuable time saved for the transplant teams to minimize CIT. The gained experience implementing an in-house technique was crucial when expanding cDCD outside our hospital using a mobile NRP team covering travel distances up to 250 km.

CONCLUSIONS

The results indicate that NRP can be an effective method to restore abdominal organ perfusion and help increase the number of grafts obtainable for transplantation. Controlled DCD provides an opportunity to pursue organ donation in clinical settings where DBD is not possible, thereby providing the patients with the option of fulfilling their last will. The introduction of well-established selection criteria of DCDs worldwide is likely to increase significantly the pool of good quality organs for transplantation. Further studies are required to fully assess the impact on organ recovery rate and results in Norway.

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