

Kidney transplant utilising donors after circulatory death: The first report from the African continent

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Background. At Groote Schuur Hospital in Cape Town, South Africa, the number of deceased organ donors has declined over the past 2 decades, necessitating a more liberal approach to donor selection. In 2007, measures to expand the deceased kidney donor pool were implemented, including an HIV positive-to-positive transplant programme and the utilisation of extended-criteria donors as well as donors after circulatory death (DCDs).

Objectives. To report on our institutional experience with DCD kidney transplants and to encourage this approach among other African centres to improve access to transplantation.

Methods. An observational cohort study of consecutive DCD kidney transplants at Groote Schuur Hospital over a 17-year period was performed. Primary endpoints were 1-, 2- and 5-year graft and patient survival. Secondary endpoints included the incidence of delayed graft function (DGF), 30-day morbidity, length of stay, and donor and recipient clinical characteristics.

Results. Fifteen DCD procurements were performed, with no kidneys discarded. Thirty kidney transplants were performed, with a median (interquartile range) cold ischaemic time of 11.5 (8 - 14) hours. The incidence of DGF was 60.0%, and 30-day morbidity (other than DGF) was 20.0%. Graft survival at 1, 2 and 5 years was 100%, 96.0% and 73.7%, respectively. Patient survival at 1, 2 and 5 years was 93.3%, 93.3% and 88.4%, respectively.

Conclusion. Long-term graft and patient survival was comparable with the international literature. DCD may present a unique opportunity to expand deceased donation throughout Africa, particularly in areas affected by a lack of brain death legislation and religious or cultural objections to donation after brain death.

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In South Africa (SA), ~3 500 patients with end-stage kidney disease are awaiting kidney transplantation.^[1] Unfortunately, SA has one of the lowest deceased organ donor rates in the world (1.6 donors per million population).^[2] Living-donor kidney transplant programmes have not been able to bridge the gap between organ supply and demand, and waiting lists continue to grow. At Groote Schuur Hospital in Cape Town, the number of deceased donors has declined over the past 2 decades,^[3] necessitating a more liberal approach to deceased-donor selection. In 2007, measures to expand the deceased kidney donor pool were implemented, including an HIV positive-to-positive transplant programme^[4] and the utilisation of extended-criteria donors (ECDs) as well as donors after circulatory death (DCDs).

Initial registry data from the UK^[5] and the USA^[6] identified a trend towards higher primary non-function (PNF) rates in kidney transplants utilising DCDs compared with donors after brain death (DBDs). Delayed graft function (DGF), defined as the need for dialysis within 7 days of transplantation, is twice as likely to occur compared with transplants from DBDs.^[7,8] Despite these observations, the literature has conclusively shown that DGF does not influence long-term graft survival.^[9,10] Kidney transplantation from DCDs has been shown to provide a survival benefit compared with waiting on dialysis for a kidney transplant from a DBD,^[11] and 1-, 5- and 10-year patient survival is comparable to DBD recipients.^[12]

Despite the successful implementation of DCD programmes across Europe and the USA,^[5,6] other SA transplant centres have not yet adopted this mode of donation.^[13] We consider that DCD has an important role to play in allowing more patients and families to support organ donation and improving access to transplantation.

The aim of the present study was to report on a low-volume institutional experience with DCD kidney transplants in a low- to middle-income country, and to encourage other African transplant centres to support this mode of donation.

Methods

This was an observational cohort study of consecutive controlled DCD kidney transplants performed at Groote Schuur Hospital and Red Cross War Memorial Children's Hospital, both tertiary referral hospitals in Cape Town, SA. Approval was obtained from the Departmental Research Committee (ref. no. DRC2017/140) and the Human Research Ethics Committee at the University of Cape Town (ref. no. HREC053/2018). This approval permitted access to prospectively maintained donor referral and kidney transplant registries to capture clinical data on DCD referrals, donor characteristics and recipient outcome in transplants from 1 January 2007 to 30 June 2023. Folder reviews were selectively performed in cases where registry data were incomplete. Informed

consent for folder review was waived. All data were anonymised prior to statistical analysis. None of the transplant donors were from a vulnerable population, and all donors' next of kin provided written informed consent for kidney donation that was freely given.

The primary endpoints were 1-, 2- and 5-year graft and patient survival. Secondary endpoints included the incidence of DGF, 30-day morbidity, length of stay, and donor and recipient clinical characteristics. The distributions of each variable were explored using histograms for continuous variables and tabulations for categorical variables. Continuous variables were summarised as means with standard deviations or medians with interquartile ranges (IQRs), depending on the distribution of data. Donor and recipient demographic and clinical characteristics were summarised as medians with IQRs for continuous variables and frequencies and percentages for categorical variables. Cumulative incidence was calculated for events of interest as number of patients with event divided by the total of DCD transplants during a specified period. The Kaplan-Meier method was used to estimate and plot graft (censored for death with functioning graft) and patient survival probability at 1, 2 and 5 years. Analysis was performed in Stata 14 (StataCorp, USA). Results were reported according to STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.

Results

Donors

Two hundred and twenty-nine patients who had sustained a variety of non-survivable central neurological insults were referred to the on-call transplant co-ordinators for assessment. The causes of neurological insult were mainly trauma related ($n=155$ patients; 67.7%). In all cases, the decision to withdraw life-sustaining therapy (WLST) was made by the treating physician or clinical team independently when it was felt that further care would be futile and that palliation with compassionate extubation, in consultation with the family, would be in alignment with the patient's wishes. Of the 229 patients referred, 80 were assessed as suitable for DCD, with 21 families or next of kin consenting to donation (26.3%). In 2 consented patients, theatre could not be accessed within a reasonable timeframe that matched the palliation timeline and donation could not take place. One consented patient had a cardiac arrest shortly after conclusion of the consent process and prior to WLST. Three patients failed to have a cardiac arrest within 1 hour of WLST, and palliative symptom management was continued by the treating physician or clinical team after the theatre team stood down as per DCD protocol. Fifteen donors (14 adults and 1 child) underwent successful kidney procurement, with no organs being damaged or discarded. Most of the donors were young, with a median (IQR) age of 22 (10 - 32) years. None of the donors fulfilled the criteria for ECD. DCD kidney donor characteristics are set out in Table 1.

Recipients

All procured kidneys were allocated to local recipients based on a negative complement-dependent cytotoxicity T- and B-cell crossmatch test. A total of 30 kidney transplants (28 adults, 2 children) were performed, with a median (IQR) cold ischaemic time (CIT) of 11.5 (8 - 14) hours. Twenty-two recipients had ≥ 6 human leucocyte antigen (HLA) mismatches. Two recipients had had a previous transplant, and 2 HIV-positive recipients were transplanted with kidneys from an HIV-positive donor (Table 2).

All recipients commenced antimetabolite therapy (19 azathioprine, 11 mycophenolic acid) on the day of the transplant. The first 5 recipients in the series did not receive induction immunosuppression, with immediate introduction of a calcineurin inhibitor (CNI) on

the day of the transplant. Subsequently, all patients received an induction immunosuppressive agent; 16 received antithymocyte globulin and 9 received basiliximab, with delayed introduction of the CNI if signs of immediate graft function were not present. Ultimately, 15 patients received cyclosporine and 15 received tacrolimus as CNI therapy. Immediate graft function was evident in 12 recipients, with 18 recipients needing at least one session of haemodialysis post-transplant, resulting in a DGF rate of 60.0%. The median (IQR) number of dialysis days in the DGF group was 10 (7 - 12). Fifteen patients (50.0%) underwent an allograft biopsy within 30 days, with acute tubular necrosis being diagnosed in 10 of the 15 biopsies (66.6%). Other histological diagnoses included acute cellular rejection ($n=1$), borderline rejection ($n=1$), ascending pyelonephritis ($n=1$), CNI toxicity ($n=1$) and normal allograft kidney ($n=1$). The overall median (IQR) length of stay was 16 (11 - 26) days, with a median of 19 (13 - 28) days in those who experienced DGF and 14 (10 - 19) days in those who did not. Thirty-day morbidity (excluding DGF) was 20.0%, which included surgical site infection ($n=1$), intra-abdominal sepsis ($n=1$), ureteric complication ($n=1$), graft pyelonephritis ($n=1$), acute cellular rejection ($n=1$) and CNI toxicity ($n=1$).

Three further patients presented with biopsy-proven acute cellular rejection within the 1st year post-transplant, with all demonstrating a clinically complete response to short-course intravenous steroid therapy. One patient who did not receive isoniazid prophylaxis developed pulmonary tuberculosis within a year post-transplant but recovered well after 6 months of first-line antituberculosis therapy. Five patients developed new-onset diabetes within the first 2 years post-transplant. Nine patients underwent allograft biopsies between 2 and 5 years post-transplant, which revealed CNI toxicity ($n=4$), acute cellular rejection ($n=2$, of whom 1 was a patient who had had biopsy-proven acute cellular rejection within 30 days post-transplant), antibody-mediated rejection ($n=1$) and pyelonephritis ($n=2$). Graft survival was 100%, 96.0% and 73.7% at 1, 2 and 5 years post-

Table 1. DCD kidney donor characteristics

Donors, <i>N</i>	15
Referral centre, <i>n</i>	GSH 14, RCWMCH 1
Age (years), median (IQR)	22 (10 - 32)
Trauma/medical ratio	5.5/1
Extended criteria, <i>n</i>	0
Vasopressor-dependent, %	53.3
Terminal sCr ($\mu\text{mol/L}$), median (IQR)	86 (73 - 181)
Discard rate, <i>n</i>	0

DCD = donor after circulatory death; GSH = Groote Schuur Hospital; RXWMCH = Red Cross War Memorial Children's Hospital; sCr = serum creatinine.

Table 2. DCD kidney recipient characteristics

Recipients, <i>N</i>	30
Age (years), median (IQR)	31 (26 - 45)
Sex, <i>n</i>	Men 19, women 11
Dialysis modality, <i>n</i>	HD 26, PD 4
Retransplant, <i>n</i>	2
HIV positive, <i>n</i>	2
HLA mismatches, <i>n</i>	
≥ 6	22
≥ 4	29
≥ 2	30

DCD = donor after circulatory death; HD = haemodialysis; PD = peritoneal dialysis; HLA = human leucocyte antigen.

transplant, respectively, and was censored in those who died with a functioning graft (Fig. 1). Three graft failures were attributed to rejection and 3 to chronic allograft nephropathy, and the exact cause was not documented in 3 cases. Patient survival was 93.3%, 93.3% and 88.4% at 1, 2 and 5 years, respectively (Fig. 2). Three patients succumbed to sepsis, 1 patient died in a motor vehicle accident, and 3 patients were not reaccepted for haemodialysis after allograft failure. Two patients were lost to follow-up.

Discussion

Considering the infrequent nature and low volume of DCD kidney transplants at our facility, the long-term patient and graft survival in our series was acceptable. Our study was not designed to compare outcomes between DCD and DBD recipients, as several meta-analyses have explored this area with consistent results.^[14,15]

The most recent meta-analysis that compared graft and patient outcome in DCD v. DBD reported that long-term (5- and 10-year) graft and patient survival for the two were similar.^[15] However,

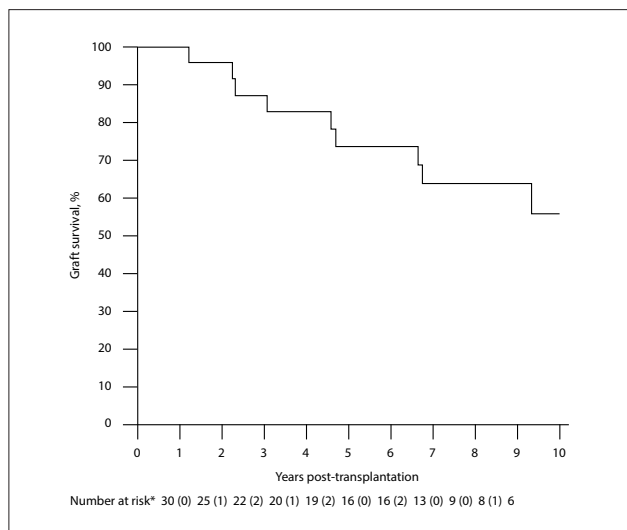


Fig. 1. Graft survival. (*Numbers in parentheses refer to the number of grafts lost during that year. The total number at risk also decreased as patients were lost to follow-up or end dates were reached.)

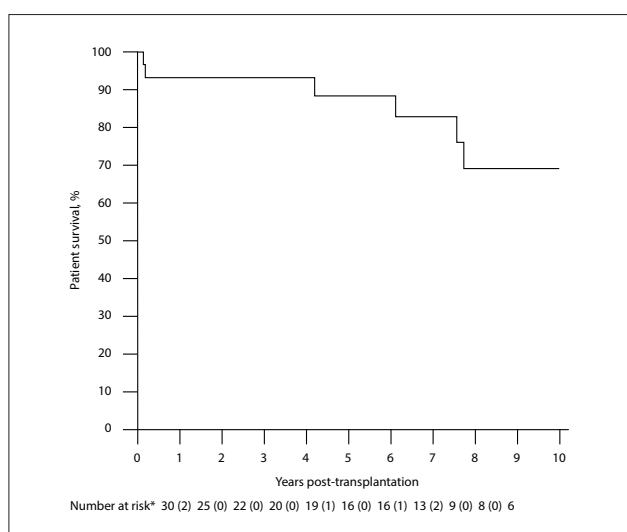


Fig. 2. Patient survival. (*Numbers in parentheses refer to the number of patients lost during that year. The total number at risk also decreased as patients were lost to follow-up or end dates were reached.)

the short-term graft and patient outcomes were different, as DCD transplants were associated with a 1.1 times increased risk of death-censored graft loss and mortality at 1 year. The pooled results from 21 studies were analysed for PNF, and DCDs were found to have a 1.43 times greater risk of PNF, which the authors thought could adequately explain the inferior 1-year graft survival compared with DBDs.^[15] Potential confounders regarding the increased 1-year mortality were identified, as most of the reports originated from the USA, where donor-recipient longevity matching has been performed since 2014. In the US allocation system, DCD donor status increases the kidney donor profile index and may result in allocation to patients with shorter estimated life expectancy.^[15]

In our series, there were no incidents of PNF. Although an increased risk of PNF is expected in all DCDs, uncontrolled DCDs seem to be at particularly high risk of PNF compared with controlled DCDs.^[16,17] The current DCD policy at our institution only allows for controlled DCD to be performed, and the relatively young donor profile in our series may partly explain why we have not observed an episode of PNF.

DGF is a well-known complication and has been shown to be mainly responsible for the increased cost associated with DCD transplants.^[18] The risk of DGF has been reported to be approximately twice that of DBD cohorts.^[15] Initial reports found that DGF did not significantly affect long-term graft survival.^[9,10] Subsequently, some contradictory reports regarding the impact of DGF on graft survival were published.^[16,17] However, the highest level of evidence in the form of a recent meta-analysis has again confirmed that DGF does not significantly influence graft survival.^[14]

In our series, 60.0% of the recipients developed DGF, which is high compared with countries with well-established DCD programmes. Although the allocation policy encouraged local allocation to minimise CIT, the median CIT ended up being relatively long at 11.5 hours. In comparison, the median CIT reported in a previous DBD series of 130 recipients from our institution was 10 hours.^[19] A major limitation of our study was that the functional warm ischaemic time was not routinely documented. Functional warm ischaemic time is the time when either the systolic blood pressure is <55 mmHg or the peripheral saturation is <70%, and is considered to be the significant time period of organ damage during the dying process.^[20] Other possible explanations may include a high incidence of donor vasopressor requirements (53.3%), and an initial learning curve with the procurement technique, as there was a decreasing trend in DGF as our experience increased.

An increased risk of urological complications in the form of urine leak or ureteric stenosis has previously been described in DCD kidney recipients.^[21,22] This does not seem to be an area of interest for current investigators, and in our series 1 patient suffered a urological complication.

The literature seems to be divided on the risk of acute rejection in DCD v. DBD. While one meta-analysis reported significantly fewer acute rejection episodes in the DCD cohort (9.5 v. 17%),^[14] others have found no association between biopsy-proven allograft rejection (BPAR) and DCD.^[15] These contradictory reports may be partially explained by the variability in defining rejection (acute rejection v. BPAR), timing of the episode (at 3 months v. 1 year), and immunosuppressive regimens.

We have found that support to refer patients for DCD has been variable and is often reliant on individual healthcare workers' knowledge of DCD and comfort in instituting palliative care, rather than being part of a formalised hospital-based initiative to improve end-of-life care. DCD referrals at our institution accounted for 15.1% of the potential donor referrals over a 17-year period (229 DCDs,

1 290 DBDs). In the UK, 40% of deceased organ donors are DCDs.^[23] In the present study, a high number of referrals ($n=149$) were excluded because they were either medically unsuitable or not able to be identified. A previous report from our unit indicated a slightly lower consent rate in DCD compared with DBD, but the difference was not statistically significant (26.3% v. 33.4%; $p=0.248$).^[24]

Challenges in the practice of DCD include identification and referral of patients as suitable potential DCD donors, supporting and maintaining the trust of bereaved families, integrating the specialist transplant nurse into the clinical teams managing the end-of-life process, and how to manage the consequences of warm ischaemia in a fashion that is professionally, ethically and legally acceptable.^[25] DCD offers a unique way forward for countries that have not yet embarked on deceased donation. Because of the lack of legislation surrounding donation after brain death in several African countries, DCD may provide an important opportunity to establish and improve access to transplantation across the continent. DCD may be culturally more acceptable to patients' families, as the donor appears dead, and the concept of circulatory death may be more acceptable than brain death.

Conclusion

Results from this study reaffirm the potential of DCD to ameliorate donor shortages throughout SA, and may be of particular relevance when religious or cultural objections to donation after brain death are commonplace.

Declaration. None.

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