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Renal Transplantation from Donation After Circulatory Death Donors: Evolution of Strategies

Editorial

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Donation after circulatory death (DCD) donors are admitted in the intensive care units, who either do not fulfil the brain-stem death criteria or in whom the withdrawal of treatment is planned because of futility of further treatment. The initial renal function and log-term outcomes of DCD renal transplantation (RT) have been a subject of concern in the transplant community because of associated deleterious effects of existing co-morbidities in the donor, elderly age and prolonged warm and cold ischaemia times [1, 2]. However, based on the enhanced understanding of the pathophysiology of DCD and experience gained over the past two decades, DCD RT has become a routine and proven a useful source of organs for transplantation. The editorial summarises the evolution of the strategies adopted to improve the outcomes of DCD RT worldwide over the past two decades.

Formerly known as non-heart beating or asystolic donors, DCD donation was introduced and succeeded in a regular basis in Maastricht by Kootstra et al., in 1989 [3]. Donors are classified as uncontrolled donors (brought in dead, unsuccessful resuscitation or cardiac arrest in hospital patient) or controlled donors (awaiting cardiac arrest or cardiac arrest after brain-stem death) [4-6]. In recent years, marked increase in DCD donation rate (per million population) has occurred in the United Kingdom (12.0), United States of America (6.3), Belgium (6.1), Spain (5.3) and Argentina (3.1) [7].

The process of organ donation for DCD has been standardised based upon the understanding of the impact of cardiorespiratory arrest on organ dysfunction and subsequent immunological events. The time allowed after withdrawal to total circulatory arrest (time-to-death; TTD) for DCD has been accepted as 2 hours, which, in one study, showed similar incidence of delayed graft function (DGF) (50.2% vs 50%), 5 year graft survival (74.1% vs 83.9%; p=0.9) and patients survival (88.8% vs. 83.9%; p=0.66) when compared with TTD of 0-1 hour [8]. The haemodynamic measurements, systolic blood pressure (SBP) and oxygen saturation of the donor during the withdrawal period has a significant influence and is predictive of DGF and graft survival. In a study including 1050 kidneys from 566 donors, the SBP was predictive of DGF (OR 1.42) and the slope of oxygen saturation during the first 10 minutes after extubation was associated with 5-year graft survival of 70.0% for donors above the median versus 61.4% for those below the median failure (below median; hazard ratio 1.30) [9].

During the retrieval surgery, use of double-balloon triple lumen catheter facilitates in situ perfusion of the organs with cold preservative solution, which has significant impact on the incidence of primary non-function (PNF) [10]. A study from UK on the effects of the type of preservation fluids such as Marshall's (hyperosmolar citrate) and University of Wisconsin solution on the incidence of DGF, PNF, biopsy-proven acute rejection (BPAR), renal function and graft survival at one year were not significantly different. Use of Marshall's solution was associated with significant cost-saving [11].

From the Dutch Organ Transplantation Registry, the outcomes in uncontrolled (Maastricht categories I and II) and controlled (Maastricht category III) DCD RT were examined, which showed significantly high incidence of PNF in uncontrolled DCD group (19.6% vs 96%; $p \leq 0.001$); DGF rate and estimated glomerular function rate (eGFR) after 1 and 5-year were comparable between the two groups when censored for PNF [12]. Because of high incidence of PNF, majority of transplant centres are reluctant to utilise kidneys from uncontrolled DCD donors.

The outcomes and cost-effectiveness of types of immunosuppressive agents have been evaluated in DCD RTs. In a study from the UK, induction with basiliximab and anti-thymocyte globulin (ATG) showed a significant lower rate of DGF, BPAR, infections requiring re-admission and a remarkable cost savings in the ATG-induced group [13]. The patient survival, graft survival, BPAR, eGFR did not differ between DCD RT recipients treated with alemtuzumab versus basiliximab or ATG. There was a trend to-

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wards reduced graft - and patient survival and increased incidence of cytomegalovirus and BK-virus infections in the alemtuzumab-treated group [14]. The phase III BENEFIT-EXT study assessed belatacept, versus cyclosporine in extended criteria deceased donor RTs and showed better renal function (4-7 mls/min higher mean eGFR in the belatacept group), but the BPAR, graft and patient survivals and infections were similar. The incidence of PTLD was high in the belatacept group [15].

Delayed graft function is an established complication after DCD kidney transplants, which prolongs hospital stay and impacts graft outcomes [16]. The impact of DGF on graft outcomes was examined by a paired door kidney analysis of data from Australia and New Zealand Dialysis and Transplant Registry (ANZDTR). Of the 74 pairs of DCD kidneys followed for a median of 1.9 years, 14% recipients with DGF had experienced overall graft loss compared to 4% in those without DGF (p=0.04; HR 4.31). The adjusted HR for BPAR and all-cause mortality at 3 years in recipients who have experienced DGF were 0.98 (95% CI 0.96, 1.01) and 1.70 (95% CI 0.36, 7.93), respectively, compared to recipients without DGF. Strategies aimed to reduce the risk of DGF could potentially improve graft survival in DCD kidney transplants [17].

Prolonged cold ischaemia time (CIT) is a known risk factor for DGF and has important implication for organ allocation policies. Analysis of data from ANZDTR, 24.6% experienced DGF and 33.9% experienced allograft loss over a median follow-up of 5.3 years. Recipients with total ischaemia time >/-14 hours experienced an increased risk of DGF, particularly with older DCD grafts. There was on average, a 9% increase in the overall risk of graft loss per hour increase in the total ischaemic time [p = 0.02] in recipients with older DCD grafts [18]. Logistic factors influencing the CIT was assessed prospectively in the UK by Shrestha et al., on 1763 RTs and identified DCD donors, transport time, cross-matching, recipient factors, virtual cross-match and availability of operating time as the determinants of CIT, which were modifiable [19].

The anticipation of compromised outcomes of DCD RT does lead to reduced acceptance of DCD donors by transplant centres, particularly when additional features of extended criteria donors (ECD) are present. Evaluation of data from Scientific Registry of Transplant Recipients on ECD/DCD donors showed higher kidney donor risk index among discarded versus transplanted kidneys (1.82 vs. 1.67; p=0.001). The adjusted odds ratios for discard were higher among donors who were older, diabetic, AB blood type, and hepatitis C positive [20].

A report from the UK showed 49% incidence of DGF in DCD RT, which is similar to previous reports. There was no difference in the 3-year patient (91.4 vs. 92.2%) and graft (88.2 vs. 90.0%) survival between DCD and DBD kidneys. The incidence of PNF was higher for the DCD than for DBD kidneys (4% vs. 3%; p=0.04). By far, kidneys from donors > 60 years had more than twice the risk of graft failure within 3 years of RT compared with those transplanted with kidneys from donors < 40 years (HR 2.35, p<0.0001) [21].

Since Kootstra et al., introduced machine preservation of DCD kidneys [22], the optimum method of preservation of DCD kidney using static cold storage (CS) or hypothermic machine perfusion (MP) was assessed in an international randomised controlled trial from Europe, which did not show significant difference in the incidence of DGF between the two methods of storage [23]. Follow-up of the recipients from the same study did not show significant difference in the three-year graft survival between the two methods of storage [24]. A multicentre randomised trial conducted in the UK for DCD kidneys, showed no difference in the incidence of DGF (58% vs. 56%), renal function at 3 and 12 months, graft and patient survival; thus concluding MP offered no advantage over CS and the latter was cheaper and more straightforward [25]. A systematic review suggested that hypothermic MP reduces DGF compared with static cold storage. There was no difference in PNF, BPAR, long-term renal function or patient survival [26].

There are a few isolated case reports on the efficacy of *Ex vivo* normothermic perfusion, where kidneys, declined by several centres previously on the ground of inadequate in situ perfusion, were perfused with oxygenated packed red cells for 60 minutes *Ex vivo* and transplanted with successful outcomes, which needs further investigation [27]. Dual kidney transplantation from adult DCD and other extended criteria donors, which otherwise might be discarded, have shown excellent medium-term outcomes and achieved reduction in waiting time particularly in older recipient population [28].

Organ shortage remains the biggest challenge in organ transplantation. To address this, special attention needs to be paid to encourage utilisation of DCD donors, modify the risk factors those influence the short-and long-term outcomes and step forward in development and optimisation of uncontrolled DCD donor programmes [29]. It is prerequisite to develop and adopt best practice guidelines for DCD in every transplant programme, which should include the decision to withdraw or limit life-sustaining in a controlled DCD setting or cessation of cardiopulmonary support in an uncontrolled DCD donation, which should be based on the patient's best interest [30].

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