Lessons Learned from a Single Center’s Experience with 134 Donation after Cardiac Death Donor Kidney Transplants

Alan C Farney, MD, PhD, Michael H Hines, MD, FACS, Samer al-Geizawi, MD, Jeffrey Rogers, MD, FACS, Robert J Stratta, MD, FACS

BACKGROUND: Reports of kidney transplantation from donation after cardiac death (DCD) donors describe high rates of delayed graft function (DGF).

STUDY DESIGN: From April 1, 2003 to October 17, 2010, we performed 134 kidney transplants from DCD donors including 120 (90%) from standard-criteria donors (SCDs) and 14 (10%) from expanded-criteria donors (ECDs). Nineteen kidneys were recovered from donors managed with extracorporeal interval support for organ retrieval (EISOR) after cardiac arrest to minimize ischemic injury.

RESULTS: Comparison of donor and recipient characteristics found no differences for cases managed with or without EISOR. Overall actuarial patient survival rates were 93%, 91%, and 89% at 1, 3, and 5 years, respectively, with a mean follow-up of 31 months. Overall actuarial kidney graft survival rates were 89%, 76%, and 76% at 1, 3, and 5 years, respectively. Actuarial graft survival rates of DCD ECD kidneys were 58% and 48% at 1 and 3 years, compared with 90% and 79% at 1 and 3 years for non-ECD grafts (p < 0.013). DGF occurred in 73 patients (54%) overall and was reduced from 55% to 21% (p = 0.016) with the use of EISOR in locally recovered kidneys. The mean resistance value on machine perfusion and the mean estimated glomerular filtration rate 1 month after transplantation were both improved (p < 0.05) in kidneys from donors managed with EISOR. Mean initial hospital stay was reduced from 8.0 to 5.0 days in patients receiving kidneys recovered with EISOR (p = 0.04).

CONCLUSIONS: EISOR is associated with a lower rate of DGF, lower graft resistance on machine perfusion, and shorter initial hospitalization. Kidneys from DCD SCDs have excellent medium-term outcomes and represent an important means of expanding the donor pool. Kidneys from DCD ECDs have inferior outcomes. (J Am Coll Surg 2011;212:440–453. © 2011 by the American College of Surgeons)

For patients with end-stage renal disease, kidney transplantation offers both additional years and improved quality of life. At the end of 2010, the United Network for Organ Sharing (UNOS) national waiting list for solid organ transplantation is approaching 120,000 registrations, including nearly 95,000 patients awaiting kidney or simultaneous kidney-pancreas transplantation. Median waiting times for kidney transplantation range from 600 to 2,000 days depending on geographic region and blood type. To address the growing disparity between organ supply and demand, recent efforts to increase the donor organ pool have incorporated the use of donors considered to be less than optimal, including older donors, donation after cardiac death (DCD) donors, and donors with comorbidities that are potentially detrimental to long-term graft survival. Fueled by National Organ Donation Breakthrough Collaborative initiatives and an Institute of Medicine report, expansion in DCD organ donation has occurred primarily in the controlled DCD donor (Maastricht category III and IV) setting.

Compared with organs from donors who meet brain death criteria (donation after brain death), DCD or nonheart-beating donor organs are inevitably subjected to variable periods of warm ischemia after withdrawal of life support.
Abbreviations and Acronyms

BMI = body mass index
CIT = cold ischemia time
CMV = cytomegalovirus
DCD = donation after cardiac death
DGF = delayed graft function
ECD = expanded-criteria donor
EISOR = extracorporeal interval support for organ retrieval
MDRD = Modification of Diet in Renal Disease
SCD = standard-criteria donor
UNOS = United Network for Organ Sharing
WIT = warm ischemia time

Support followed by declaration of death by cardiocirculatory arrest with subsequent organ recovery.7-9 It is well established that prolonged warm ischemia is associated with acute tubular necrosis, irreversible cell damage, and reduced graft survival after kidney transplantation.9-11 In spite of the terminal warm ischemia inherent in the DCD donor organ recovery process, numerous studies suggest that transplant outcomes, such as short- and medium-term patient and graft survival rates, appear to be similar between donation after brain death standard-criteria donors (SCD; <50 years or 50–59 years of age without additional risk factors) and DCD donor kidney grafts, but delayed graft function (DGF) is more common for transplanted DCD donor kidneys.12-21 In the non-DCD donor setting, the detrimental impact of DGF is well documented.9-11,22 Compared with kidneys with immediate graft function, the presence of DGF doubles the rate of graft loss at 5 years’ follow-up. Although the precise contribution of DGF to kidney graft loss is debated, many studies have identified DGF as a risk factor for acute rejection, increased resource utilization, and diminished medium-term graft survival in recipients of donation after brain death donor kidneys.9,10,11,22

Despite the increased incidence of DGF, initial concerns about the prognosis of kidney transplantation from DCD donors have lessened.12-21 As centers have gained increased experience and more confidence in transplanting DCD donor kidneys, DCD donor acceptance criteria have been liberalized to include expanded-criteria donors (ECD) as well as donors with acute renal failure.23 However, the value of using DCD ECD kidneys remains uncertain, owing to concerns regarding the immediate and long-term outcomes of these grafts, particularly in the setting of DGF. Proper assessment of DCD donors, optimal methods of recovery and preservation, appropriate recipient selection and immunosuppression, and minimization of ischemia-reperfusion injury remain key issues in DCD organ transplantation. Two recent “randomized” studies of machine perfusion preservation in DCD kidney transplantation reported opposite conclusions regarding the efficacy of machine perfusion in reducing the incidence of DGF in DCD kidneys.24,25 Moreover, in both of these studies, the incidence of DGF was >50% with either machine or cold storage preservation. Preliminary experience with extracorporeal support as a means to reduce ischemic injury and DGF in DCD donors has been promising, although application of this technology is limited to date.17,26-31 The purpose of the present study was to review retrospectively our 7-year experience in DCD kidney transplantation with an emphasis on a number of lessons learned, including the influence of prolonged warm and cold ischemia, the impact of DGF, the role of machine perfusion selective use of extracorporeal support, our experience with DCD ECDs, and appropriate recipient selection, in an attempt to optimize outcomes.

METHODS

Study design

This is a single-center retrospective review of all adult (age ≥19 years) DCD kidney and simultaneous kidney-pancreas transplantations that were performed at our center between April 1, 2003, and October 17, 2010. Our study comprised only controlled (Maastricht category III) DCD kidney transplants in which organ recovery occurred after the donor was declared dead by cardiocirculatory arrest after planned withdrawal of life support. For study purposes, we stratified our overall DCD experience according to DCD SCD and DCD ECD kidney transplants as well as those kidneys recovered from donors managed with or without extracorporeal interval support for organ retrieval (EISOR).17 Donation after brain death and living donor kidney transplants as well as pediatric recipients (age <19 years) were excluded from the analysis.

Definitions

ECDs were defined by UNOS criteria as all deceased donors aged ≥60 years or donors aged 50–59 years with any of the following 3 specific comorbid conditions: brain death from cerebrovascular accident, history of hypertension, or a serum creatinine level >1.5 mg/dL.5,6 All adult deceased donors were considered to be SCD unless they met the ECD definition.32 DGF was defined as the need for dialysis for any reason in the first week following transplantation.8,11 Renal allograft loss was defined as death with a functioning graft, allograft nephrectomy, resumption of dialysis, retransplantation, or return to the pretransplant serum creatinine level. Primary nonfunction was defined as the failure to render the patient dialysis free after kidney transplantation, absence of a decline in serum creatinine level in a preemptively transplanted patient, or early
allograft nephrectomy after transplantation. Warm ischemia time (WIT) was defined as the time after withdrawal of life support from when the potential donor developed significant ischemia (such as either an oxygen saturation <80% or a systolic blood pressure <80 mmHg [mean arterial pressure <60 mmHg]) until in situ flushing of organs. For donors managed with EISOR, WIT was the time from significant ischemia (as defined above) after withdrawal of life support to the initiation of EISOR after declaration of death by cardiocirculatory arrest. Cold ischemia time (CIT) was defined as the period of time from aortic cross-clamping with initiation of cold in situ flushing in the donor to the time of kidney revascularization in the recipient. CIT incorporated not only the time of organ removal in the donor but also cold storage ex vivo, machine perfusion (when applicable), bench preparation of the kidney, and the anastomosis time in the recipient. A DCD donor was any donor who did not meet standard brain death criteria or who developed cardiac arrest before organ recovery. DCD donors were managed according to the algorithms outlined below.17,27,33,34

Donor evaluation and management

The donor consent process and medical management were independently carried out by the donor organ procurement organization. Vital signs (blood pressure, heart rate and rhythm, respiratory rate, and transcutaneous oxygen saturation) were monitored after withdrawal of life support until asystole occurred. Cardiac death was declared after 5 minutes of asystole, and rapid organ recovery ensued in the absence of EISOR. The recovery technique most commonly used for DCD was open midline laparotomy and sternotomy with direct aortic cannulation and in situ perfusion with cold preservation solution combined with topical cooling. A total of 19 kidneys (including 5 simultaneous kidney-pancreas transplantations) came from DCD donors at our center managed with EISOR, but not all DCD organs managed with EISOR were transplanted at our center. In DCD cases supported with EISOR, families consented to vascular cannulation of the femoral vessels and systemic heparinization before withdrawal of life support. After 5 minutes of asystole and declaration of death by cardiocirculatory arrest in the intensive care unit, donors were cooled to 22°C and perfused with oxygenated blood at 4–6 L/min flow rates using the EISOR circuit. After initiation of EISOR, the donor was transported non-urgent to the operating room where multiple organ procurement (including liver and pancreas in selected cases) was performed using standard techniques similar to those for donation after brain death donors. Donors were typically managed on the EISOR circuit for 1–2 hours during the organ recovery process, after which time the same circuit was used for rapid infusion of preservation solution and exsanguination.17

Specific criteria were used to accept kidneys for DCD compared with donation after brain death donors. Absolute contraindications for use of DCD kidney(s) included: admission donor estimated creatinine clearance <70 mL/min (using the Cockcroft-Gault formula), malignancy, HIV-positive serology; CIT >45 hours; WIT >90 minutes in an SCD and >60 minutes in an ECD, machine perfusion flow ≤60 mL/min or resistance ≥0.4 mmHg/mL/min, and biopsy findings such as >15% glomerulosclerosis or moderate vascular, tubular, or parenchymal changes. For pediatric DCD donors, the machine perfusion parameter thresholds were a flow >50 mL/min and a resistance <0.4 mmHg/mL/min. High risk for viral transmission (meeting Centers for Disease Control criteria) was considered to be a relative contraindication to organ acceptance, and the needs of the potential recipient were weighed against the particular risks of the donor. All DCD kidneys underwent biopsy, and an attempt was made to place all DCD kidneys on machine perfusion for a minimum of 6 hours.

Recipient selection

Recipients were selected for transplantation based on UNOS guidelines. If a potential kidney donor or kidney graft did not meet minimum requirements (see above), then the kidney was turned down for all recipients. Using the estimated donor creatinine clearance, kidneys were allocated based on nephron mass matching to predictably achieve an serum creatinine level <2.0 mg/dL in the recipient. The main consideration pertinent to the present study was an evaluation of renal function and a determination of any preexisting renal disease. This rule simply objectified our center’s strategy when deciding whether or not to accept a particular donor kidney for a specific recipient, namely, that the kidney transplant should achieve not only a dialysis-free state but also acceptable renal function to not leave the recipient exposed to the risk of complications from suboptimal immunosuppression to protect marginal renal function. In selected cases, dual kidney transplantations were performed from marginal DCD donors or donors with acute renal failure to optimize nephron mass and achieve adequate renal function in an appropriately selected recipient.

Immunosuppression

Throughout the course of the study, the maintenance immunosuppressive regimen remained constant. All patients received T-cell–depleting antibody induction consisting of either rabbit antithymocyte globulin (1.5 mg/kg intraoperatively and then every other day for a minimum of 3
or a 25% increase from baseline level and confirmed by an unexplained rise in serum creatinine level of 0.3 mg/dL or a single 30 mg intraoperative dose. After February 2005, many patients were enrolled in a randomized study comparing these 2 induction agents with the same maintenance immunosuppression regimen. Since September 2007, almost all patients received single-dose alemtuzumab induction. Mycophenolate mofetil (500 mg orally twice daily) and steroids were given from the time of transplantation. Once the depleting agent induction was completed, mycophenolate mofetil was increased to full dose (1,000 mg orally twice daily) in patients aged <60 years and kept at 500 mg twice daily in patients ≥60. Oral tacrolimus was administered twice daily after resolution of DGF or by day 7 after transplantation. Patients with persistent DGF underwent a surveillance kidney biopsy at 2 weeks after transplantation. Tacrolimus target levels and whether to withdraw steroids depended on a 2-tiered immunologic risk stratification and initial kidney graft function. Patients considered to be at higher immunologic risk (retransplants, panel reactive antibody levels >20%, African Americans <40 years of age) or those who experienced DGF remained on steroids but were tapered to 5 mg/d by 2 months after transplantation. High-immunologic-risk patients were managed with target tacrolimus levels of 10–12 ng/mL for the first 3 months after transplantation and 8–10 ng/mL thereafter. Low-immunologic-risk patients were tapered off steroids by postoperative day 6, and target tacrolimus levels were 8–10 ng/mL for the first 3 months after transplantation and 6–8 ng/mL thereafter.

**Anti-infective prophylaxis**

All patients received surgical site prophylaxis with a first-generation cephalosporin for 24 hours, antifungal prophylaxis with nystatin or fluconazole for 1–2 months, and anti-**Pneumocystis** prophylaxis with sulfamethoxazole/trimethoprim (or dapsone if allergic to sulfa) for ≥12 months. Antiviral prophylaxis consisted of oral valganclovir for 3–6 months, depending on donor and recipient cytomegalovirus (CMV) serologic status. Specifics regarding drug dosing and duration have been published previously.

**Posttransplantation management**

When appropriate, patients received aspirin prophylaxis. Treatment of hypertension, hyperlipidemia, anemia, diabetes, and other medical conditions was initiated as indicated, aiming to maintain the blood pressure <140/90 mmHg, fasting serum cholesterol <200 mg/dL, hematocrit >28%, and fasting blood sugar <126 mg/dL. The diagnosis of renal allograft rejection was suggested by an unexplained rise in serum creatinine level of >0.3 mg/dL or a 25% increase from baseline level and confirmed by ultrasound-guided percutaneous biopsy. Since March 2008, all patients underwent both reperfusion and 1-month surveillance kidney biopsies unless there was a specific contraindication. In addition, most patients underwent a 1-month follow-up biopsy after treatment of rejection to document histologic improvement.

Posttransplantation renal allograft function was evaluated by measuring serum creatinine levels as well as calculating glomerular filtration rates by using the abbreviated Modification of Diet in Renal Disease (MDRD) formula.

**Statistical analyses**

Endpoints included patient survival as well as uncensored and death-censored graft survival. Other study endpoints included DGF and renal allograft function. Data were compiled from both prospective and retrospective databases, with confirmation by medical record review in accordance with local Institutional Review Board guidelines and approval. Data were placed on an SPSS 18.0 spreadsheet for analysis. For continuous variables, univariate analysis was performed by the unpaired *t* test for normally distributed variables, and the Mann-Whitney *U* test for nonparametric distribution. For categoric variables, the chi square test was applied, and Fisher exact test was used when data were sparse. Actuarial patient and graft survival curves were also computed by using the Kaplan-Meier method and compared by using log-rank tests. Categoric data were summarized as proportions and percentages, and continuous data were summarized as means and standard deviations. A 2-tailed *p* value of <0.05 was considered to be significant.

**RESULTS**

Between April 1, 2003, and October 17, 2010, 134 renal transplantations were performed using kidneys from DCD donors. As of November 17, 2010, mean follow-up was 31 months (range 1 to 91 months). A total of 107 patients had at least 1 year’s follow-up, and 58 had at least 3 years’ follow-up. Of the 134 renal transplants, 19 kidneys (14%) were recovered from donors managed with EISOR, including 5 simultaneous kidney-pancreas transplantations (4%, Tables 1 and 2). The overall mean donor age was 40 ± 16 years (range 2–62 years), including 43 kidneys (32%) from DCD donors aged ≥50 years and 14 kidneys (10%) from DCD ECDs. The mean overall WIT was 24 ± 15 minutes. There were 40 kidneys (30%) transplanted with WIT >30 minutes, 15 (11%) with WIT >45 minutes, and 6 (5%) with WIT >60 minutes. A comparison of donor characteristics including age, terminal renal function, cerebrovascular accident as a cause of brain injury, and WIT found no differences for donors managed with or without EISOR (Table 1).
Of the 134 recipients, 56 (42%) were African American, 12 (9%) received retransplants, 10 (7%) had a panel reactive antibody level >20%, and 39 (29%) were aged ≥60 years (Table 1). Diabetes was present before transplantation in 40 recipients (30%), and 50 (37%) were considered to be obese with a body mass index (BMI) ≥30 kg/m². Recipient demographics such as age, gender, race, BMI, retransplant, panel reactive antibody level, and presence of diabetes did not differ significantly between groups managed with or without EISOR during organ procurement (Table 1).

### Table 1. Donation after Cardiac Death Donor and Recipient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All donors (n = 134)</th>
<th>Non-EISOR donors (n = 115)</th>
<th>EISOR donors (n = 19)</th>
<th>p Value (non-EISOR vs EISOR)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Donor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y, mean ± SD</td>
<td>40 ± 16</td>
<td>40 ± 16</td>
<td>38 ± 12</td>
<td>NS</td>
</tr>
<tr>
<td>Age ≥50 y, n (%)</td>
<td>43 (32)</td>
<td>39 (35)</td>
<td>4 (22)</td>
<td>NS</td>
</tr>
<tr>
<td>ECD, n (%)</td>
<td>14 (10)</td>
<td>12 (10)</td>
<td>2 (10)</td>
<td>NS</td>
</tr>
<tr>
<td>CVA cause of death, n (%)</td>
<td>20 (15)</td>
<td>19 (17)</td>
<td>1 (5)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Recipient</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y, mean ± SD</td>
<td>51 ± 14</td>
<td>52 ± 14</td>
<td>50 ± 12</td>
<td>NS</td>
</tr>
<tr>
<td>Age ≥60 y, n (%)</td>
<td>39 (29)</td>
<td>36 (31)</td>
<td>3 (16)</td>
<td>NS</td>
</tr>
<tr>
<td>BMI, kg/m², mean ± SD</td>
<td>28 ± 5</td>
<td>28 ± 6</td>
<td>27 ± 4</td>
<td>NS</td>
</tr>
<tr>
<td>BMI ≥30 kg/m², n (%)</td>
<td>50 (37)</td>
<td>44 (38)</td>
<td>6 (32)</td>
<td>NS</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>65 (49)</td>
<td>54 (47)</td>
<td>11 (58)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes as cause of renal failure, n (%)</td>
<td>40 (30)</td>
<td>32 (26)</td>
<td>8 (42)</td>
<td>NS</td>
</tr>
<tr>
<td>African American, n (%)</td>
<td>56 (42)</td>
<td>48 (42)</td>
<td>8 (42)</td>
<td>NS</td>
</tr>
<tr>
<td>Retransplant, n (%)</td>
<td>12 (9)</td>
<td>11 (10)</td>
<td>1 (5)</td>
<td>NS</td>
</tr>
<tr>
<td>Presence of PRA ≥20%, n (%)</td>
<td>21 (16)</td>
<td>20 (17)</td>
<td>1 (5)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Terminal creatinine clearance, mL/min, mean ± SD</strong></td>
<td>127 ± 57</td>
<td>128 ± 58</td>
<td>112 ± 51</td>
<td>NS</td>
</tr>
<tr>
<td><strong>WIT, min, mean ± SD</strong></td>
<td>26 ± 15</td>
<td>26 ± 15</td>
<td>22 ± 18</td>
<td>NS</td>
</tr>
<tr>
<td>WIT &gt;30 min, n (%)</td>
<td>40 (30)</td>
<td>35 (30)</td>
<td>5 (26)</td>
<td>NS</td>
</tr>
<tr>
<td>WIT &gt;45 min, n (%)</td>
<td>15 (11)</td>
<td>12 (10)</td>
<td>3 (16)</td>
<td>NS</td>
</tr>
<tr>
<td>WIT &gt;60 min, n (%)</td>
<td>6 (5)</td>
<td>5 (4)</td>
<td>1 (5)</td>
<td>NS</td>
</tr>
</tbody>
</table>

EISOR, extracorporeal interval support for organ retrieval; ECD, expanded-criteria donor; CVA, cerebrovascular accident; WIT, warm ischemia time; BMI, body mass index; PRA, panel reactive antibody.

Of the 134 transplant recipients, 56 (42%) were African American, 12 (9%) received retransplants, 10 (7%) had a panel reactive antibody level >20%, and 39 (29%) were aged ≥60 years (Table 1). Diabetes was present before transplantation in 40 recipients (30%), and 50 (37%) were considered to be obese with a body mass index (BMI) ≥30 kg/m². Recipient demographics such as age, gender, race, BMI, retransplant, panel reactive antibody level, and presence of diabetes did not differ significantly between groups managed with or without EISOR during organ procurement (Table 1).

### Table 2. Transplant Characteristics

<table>
<thead>
<tr>
<th>Transplant characteristic</th>
<th>All donors (n = 134)</th>
<th>Non-EISOR donors (n = 115)</th>
<th>EISOR donors (n = 19)</th>
<th>p Value (non-EISOR vs EISOR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIT, h, mean ± SD</td>
<td>25 ± 9</td>
<td>26 ± 9</td>
<td>19 ± 4</td>
<td>0.002</td>
</tr>
<tr>
<td>CIT &gt;30 h, n (%)</td>
<td>30 (22)</td>
<td>30 (26)</td>
<td>0 (0)</td>
<td>0.006</td>
</tr>
<tr>
<td>CMV status: D+/R−</td>
<td>19 (14)</td>
<td>16 (14)</td>
<td>3 (16)</td>
<td></td>
</tr>
<tr>
<td>0 HLA mismatch, n (%)</td>
<td>6 (4)</td>
<td>6 (5)</td>
<td>0 (0)</td>
<td>NS</td>
</tr>
<tr>
<td>Use of MP, n (%)</td>
<td>129 (96)</td>
<td>111 (97)</td>
<td>18 (95)</td>
<td>NS</td>
</tr>
<tr>
<td>Pump resistance, mmHg/mL/min</td>
<td>0.24 ± 0.1</td>
<td>0.25 ± 0.1</td>
<td>0.18 ± 0.05</td>
<td>0.005</td>
</tr>
<tr>
<td>Dual renal transplant, n (%)</td>
<td>7 (5)</td>
<td>7 (6)</td>
<td>0 (0)</td>
<td>NS</td>
</tr>
<tr>
<td>SKPT, n (%)</td>
<td>5 (4)</td>
<td>0 (0)</td>
<td>5 (26)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Local donors (same OPO), n (%)</td>
<td>94 (70)</td>
<td>75 (65)</td>
<td>19 (100)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

EISOR, extracorporeal interval support for organ retrieval; CIT, cold ischemia time; CMV, cytomegalovirus; HLA, human leukocyte antigen; MP, machine perfusion; SKPT, simultaneous kidney-pancreas transplantation; OPO, organ procurement organization.

### Patient survival

Of the 134 transplant recipients, 11 (8.2%) died during follow-up, including 7 patients who died with a functioning graft and 4 patients who died after experiencing kidney graft loss. Actuarial patient survival rates were 93%, 91%, and 89% at 1, 3, and 5 years, respectively (Fig. 1). Sepsis was the most common cause of death (4 patients, 36%), followed by cardiovascular events (3 patients, 27%), cancer (3 patients, 27%), and gastrointestinal hemorrhage (1 patient, 9%). Post-transplantation lymphoproliferative disease, lung cancer, and bladder cancer accounted for the 3...
malignancies that resulted in death. The patient with bladder cancer likely had this disease at the time of transplantation, but the other 2 cancers occurred later after transplantation. Of 11 deaths, 4 (36%) occurred in the early post-transplantation period (≤1 month), and the remainder from 8 to 40 months after transplantation. Of the 39 recipients aged ≥60, 8 (21%) died during follow-up compared with 3 deaths (3%; p = 0.0023) in younger recipients. Actuarial patient survival rates were 81%, 76%, and 69% for recipients aged ≥60 years compared with 98%, 97%, and 97%, for younger recipients at 1, 3, and 5 years' follow-up, respectively (p < 0.001). Of the 8 deaths in the older age group, 2 patients (25%) died in the early post-transplantation period and 5 (63%) died with a functioning graft. One older patient died at home 2 weeks after transplantation from a gastrointestinal hemorrhage, and another died at 1.5 months after transplantation from metastatic bladder cancer. Two younger recipients died early with functioning grafts, and the other younger patient developed graft loss 1 month before death due to sepsis. The incidence of deaths with a functioning graft was higher in older (12.8%) compared with younger recipients (2.1%; p = 0.02). Patient survival did not differ according to use of EISOR but was lower in recipients of DCD ECD (78.6%) compared with DCD SCD kidneys (93.3%; p = 0.09).

**Graft survival**

Overall actuarial kidney graft survival rates were 89%, 76%, and 76% at 1, 3, and 5 years, respectively (Fig 1). Of 134 grafts, 26 (19%) failed, including 10 due to chronic allograft nephropathy, 7 died with a functioning graft, 4 primary nonfunction, 3 acute rejection, 1 acute tubular necrosis from urosepsis, and 1 accidental embolization with infarction. Actuarial death-censored graft survival rates were 93%, 84%, and 84% at 1, 3, and 5 years, respectively. ECD status significantly influenced uncensored graft survival. Actuarial graft survival rates of DCD ECD kidneys were 58% and 48% at 1 and 3 years, compared with 90% and 79% at 1 and 3 years for non-ECD grafts (p = 0.013). Death-censored graft survival rates at 1 and 3 years were 78% and 65% for DCD ECD compared with 95% and 86% for DCD SCD kidney recipients (p = 0.17). All 7 dual renal transplants (3 ECD) continue to function as well as 3 solitary kidneys transplanted from SCDs with acute renal failure. Donor age was not an independent risk factor for graft failure, because recipients of non-ECD kidneys from donors ≥50 years old had graft survival rates of 92% and 75% at 1 and 3 years, respectively (Fig. 2). Recipients ≥60 years old had less favorable graft survival rates at 1 and 3 years (79% and 64%) compared with younger recipients (90% and 81%; p = 0.09), but much of this difference was attributable to deaths with a functioning graft, because a death-censored survival analysis showed no difference in graft survival rates between older and younger recipients. Actuarial graft survival rates of transplanted kidneys from donors managed with EISOR were 88% and 88% compared with 87% and 74% for non-EISOR kidneys at 1 and 3 years, respectively (p = 0.12; Table 3). Acute rejection occurred in 25 patients (19%) overall, including 3 (16%) and 22 (19%) recipients of kidneys from EISOR and non-EISOR donors, respectively (p = NS; Table 3).

**Graft function and effect of EISOR**

Of 134 grafts, 73 (54%) exhibited DGF and 4 (3%) had primary nonfunction (Table 3). The presence of DGF did not adversely influence graft survival, because actuarial graft survival rates were 86%, 76%, and 76% for patients with DGF compared with 92%, 76%, and 76% for patients without DGF at 1, 3, and 5 years, respectively (p =

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**Figure 1.** Overall patient and graft survival for recipients of donation after cardiac death kidneys (n = 134). Actuarial patient survival rates were 93%, 91%, and 89% at 1, 3, and 5 years, respectively. Actuarial kidney graft survival rates were 89%, 76%, and 76% at 1, 3, and 5 years, respectively (Fig 1). Of 134 grafts, 26 (19%) failed, including 10 due to chronic allograft nephropathy, 7 died with a functioning graft, 4 primary nonfunction, 3 acute rejection, 1 acute tubular necrosis from urosepsis, and 1 accidental embolization with infarction. Actuarial death-censored graft survival rates were 93%, 84%, and 84% at 1, 3, and 5 years, respectively. ECD status significantly influenced uncensored graft survival. Actuarial graft survival rates of DCD ECD kidneys were 58% and 48% at 1 and 3 years, compared with 90% and 79% at 1 and 3 years for non-ECD grafts.

**Figure 2.** Graft survival according to donor age and expanded-criteria donor (ECD) status. Actuarial graft survival rates of donation after cardiac death (DCD) ECD kidneys were 58% and 48% at 1 and 3 years, respectively, compared with 90% and 79% at 1 and 3 years, respectively, for non-ECD grafts (p = 0.013). The figure further stratifies non-ECD donor kidneys into donors >50 and <50 years of age (p = NS). Gray solid line, donor >50 y (n = 91); red dashed line, donor >50 y (not ECD, n = 29); green dotted line, DCD ECD (n = 34).
NS; Fig 3). DGF did not increase the risk of acute rejection. Of 73 recipients with DGF, 13 (18%) developed acute rejection compared with 12 (20%) recipients without DGF (pNS).

Although ECD status had a detrimental effect on graft survival, DCD ECD kidneys were not associated with either an increased rate of DGF or acute rejection (data not shown). Likewise, donor age, recipient age, and WIT had no apparent effect on the risk for DGF (Fig 4). However, 83% of kidneys with CIT >30 hours exhibited DGF compared with 45% of kidneys with CIT <30 hours (p0.001). Use of EISOR had a positive impact on the risk of DGF. Of 19 kidneys transplanted from donors managed with EISOR, only 4 recipients (21%) had DGF, compared with 69 recipients (60%) receiving kidneys transplanted from non-EISOR donors (p=0.002).

Machine perfusion was used in combination with cold storage preservation in 129 (96%) of the DCD kidneys before transplantation. The mean resistance value, measured before the kidney was removed from machine perfusion was 0.24±0.1 mmHg/mL/min overall, but 0.18±0.05 versus 0.25±0.1 mmHg/mL/min in donors managed with and without EISOR, respectively (p=0.005). Cerebrovascular accident as a cause of brain injury in the donor did not adversely influence the terminal resistance on machine perfusion. Kidneys from EISOR donors had shorter CIT (19±4 hours) compared with non-EISOR donors (26±9 hours; p=0.002), and CITs of kidneys managed without EISOR were more likely to exceed 30 hours (Table 2). Of 134 DCD donor kidneys, 94 (70%) were procured within our local organ procurement organization territory, and the remainder (imports) originated from other organ procurement organizations. Because

<table>
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*Excludes simultaneous kidney-pancreas transplantation.

EISOR, extracorporeal interval support for organ retrieval; DGF, delayed graft function; eGFR, estimated glomerular filtration rate.
EISOR was conducted only at the site of this study, the EISOR donor group was 100% “local” compared with 75 local donor kidneys (65%) in the non-EISOR group (p = 0.009). Consequently, a control group of non-EISOR donor kidneys was selected by excluding kidneys imported from another organ procurement organization and local kidneys with a CIT ≥30 hours. The resulting cohort of 53 locally recovered non-EISOR donor kidneys had a mean CIT of 21 ± 5 hours compared with 19 ± 4 hours for EISOR donor kidneys (p = NS). Of 53 kidneys transplanted from the non-EISOR local control group, 29 recipients (55%) had DGF, a rate of DGF significantly exceeding the 4 (21%) associated with use of EISOR (p = 0.016; Table 4). The mean resistance value on machine perfusion was 0.25 ± 0.1 mmHg/mL/min in the control group compared with 0.18 ± 0.05 mmHg/mL/min for kidneys from donors managed with EISOR (p = 0.004). Estimated glomerular filtration rate at 1 month after transplantation was 38 ± 18 mL/min and 50 ± 25 mL/min for the local control group and patients receiving kidneys from EISOR donors, respectively (p = 0.02; Fig 4). At 1 year, estimated glomerular filtration rate was 43 ± 19 mL/min without EISOR compared with 47 ± 24 mL/min with EISOR (p = NS). Initial length of hospital stay was 8 ± 5 days for recipients of kidneys from control donors without EISOR compared with 5 ± 1 days for patients who received kidneys from donors managed with EISOR (p = 0.04; Table 4).

**DISCUSSION**

Although overall growth for organ donation has remained static in the past 6 years, the number of organs used from DCD donors increased nearly 10-fold between 1999 and 2008.44 DCD donors now account for 10% of the overall deceased donor pool for kidneys.45 In an earlier study of 53 DCD kidney transplantations with a mean follow-up of 12 months, we found that recipients of DCD donor kidneys had similar patient and graft survival rates at 1 and 2 years compared with recipients of donation after brain death SCD kidneys and improved outcomes compared with recipients of donation after brain death ECD kidneys.37 In that study, we also determined that DCD kidneys had intermediate graft function (measured by serum creatinine and estimated glomerular filtration rate levels) compared with donation after brain death SCD and ECD kidneys. The purpose of the present study was to examine longer-term outcomes after DCD kidney transplantation, identify characteristics that result in optimal outcomes, and further explore the impact of EISOR during donor procurement.

Outcomes after DCD kidney transplantation have previously been described as inferior to donation after brain death kidney transplantation.16,34 In the present study, actuarial 5-year patient and graft survival rates for 134 DCD donor renal recipients (mean follow-up 31 months) were 89% and 76%, respectively. The actuarial death-censored graft survival rate at 5 years was 84%, indicating robust graft longevity. Although not compared prospectively to contemporaneous donation after brain death SCD kidney transplantations performed at our center during the study period (which was done in our previous study), these longer-term DCD kidney transplantation results compare favorably with our own previously published donation after brain death deceased-donor kidney transplantation outcomes as well as with outcomes of donation after brain death kidney transplantations reported to the Scientific Registry of Transplant Recipients.17,35-40 In our overall DCD kidney transplantation experience, ECD status was the most significant donor characteristic that negatively affected graft survival. Others have found that older donor age adversely influences graft outcomes after DCD kidney transplantation,41 but in our study recipients of kidneys from SCDs ≥50 years old had a graft survival rate similar to recipients of kidneys from younger SCDs at 3 years’ follow-up (75%; Fig. 2). In contrast, actuarial DCD ECD kidney graft survival was 48% at 3 years, compared with 79% for DCD SCDs (p = 0.013). All DCD ECD graft losses occurred among recipients of solitary grafts; 3 dual renal transplants from DCD ECDs continue to function.
We do not think that kidneys from DCD ECDs represent an absolute contraindication to kidney transplantation, but their use should be tempered by the realization that kidneys from DCD ECDs do not have a proven track record; the final decision to use these kidneys should be predicated on careful consideration of recipient risks and benefits with appropriate informed consent. Admittedly, the number of DCD ECDs in the present study was small (n = 14). Experience with larger numbers of DCD ECDs may help to identify characteristics (such as older donor age, prolonged WIT or CIT) that might stratify DCD ECDs into subgroups that predictably might be associated with inferior outcomes. Based on our more recent experience, we currently think that transplanting DCD ECD kidneys as dual transplants might achieve better outcomes and represent a superior way of using these organs.

There was a trend toward less favorable graft survival for recipients ≥60 years old, but a death-censored analysis showed that death with a functioning graft accounted for much, if not all, of the difference seen in graft survival based on recipient age. Patient survival was clearly lower in recipients ≥60 years old. Actuarial survival at 5 years was 69% for those ≥60 years old compared with 97% for younger recipients (p < 0.001). There was 1 early death in an older recipient which may have been related in part to DGF, which is an inherent risk of kidney transplantation from DCD donors. However, the majority of deaths in older patients were late (>8 months after transplantation) and more likely related to the consequences of immunosuppression, because malignancy and sepsis predominated as the causes of death.

This study bore out the well-known observation that DCD kidneys are at high risk for DGF. The incidence of DGF after transplantation from DCD donors is variously described as ~25% to >90%.12-20 The logical and commonly accepted explanation for the increased risk of DGF is warm ischemia, resulting in reperfusion injury, acute tubular necrosis, and graft dysfunction.9-11 Warm ischemia, though seemingly straightforward, is actually quite difficult to define. The main drawback to DCD organ donation has been the variable period of warm ischemia that occurs before organ procurement. The interval from asystole to cross-clamp and organ perfusion (agonal phase) is a straightforward and measurable parameter, but warm ischemia that occurs during the withdrawal phase before asystole is much more difficult to quantify. In the present study, warm ischemia was measured from the time of persistent systolic blood pressure <80 mmHg or oxygen saturation <80% to the time of organ flush with cold preservation solution. This definition was adopted per guidelines from our local organ procurement organization based on national consensus.33,34 For donors managed with EISOR, the end of the warm ischemia phase was marked by the start of extracorporeal perfusion. With this definition of WIT and donor selection criteria as described and previously published,17 WIT did not have a significant impact on either graft survival or DGF even though 40 kidneys were transplanted from DCD donors with WITs >30 minutes. In contrast, using a systolic blood pressure <50 mmHg to define the start of WIT and possibly different donor selection criteria, Ho and colleagues found that increased WIT did increase the risk of DGF.41 Using yet another definition of WIT, Keizer-Karin and coauthors found that WIT >30 minutes was linked to early graft failure.46 Two possibilities account for our different observation regarding the impact of WIT on outcome. First, the definition of WIT in the present study may not be sensitive or accurate enough to define inadequate organ perfusion (perhaps a lower systolic blood pressure, such as described by Ho and colleagues, should be used). Second, if the donor selection criteria limiting WIT had been more liberal, an impact of WIT on graft function might have been detected. Ideally, an accurate and consistent measurement of WIT should be applied universally so that there is optimal use of DCD organs but no substantial untoward (or irreversible) effects of prolonged WIT.

An interesting finding in the present study was that the use of EISOR in donor management was not associated with a reduction in WIT. A WIT difference of approximately 5 minutes was observed with use of EISOR, but it was not statistically, and probably not clinically, significant. One might attribute a reduction in WIT to improved graft outcomes such as better machine perfusion parameters and good initial graft function (lower rate of DGF and better estimated glomerular filtration rate at 1 month). However, the modest reduction in WIT suggests that the reduction in DGF (and improvement in pump resistance values) associated with the use of EISOR was independent of any effect on WIT. A number of earlier studies have suggested that extracorporeal perfusion in the setting of DCD donor organ recovery represents a novel method of transforming the initial period of warm ischemia into a period of ischemic preconditioning.26-31 Ischemic preconditioning has been shown experimentally to increase the energy charge and antioxidant levels in recovered organs, which may in effect resuscitate kidneys from the damaging effects of the requisite hypoxemia and ischemia inherent in the DCD donor organ retrieval process.31 This effect appears to be independent of machine perfusion which in our experience is not associated with a reduction in DGF.

The importance of DGF is generally recognized to be linked to decreased graft survival and an increased risk of rejection. DGF did not affect either graft survival or acute
rejection in the present study. The results of this study are consistent with earlier observations showing that DGF, currently defined as the need for ≥1 dialysis treatments in the first week after transplantation, does not have the same detrimental effect on graft survival after DCD as it does for donation after brain death kidney transplantation.\textsuperscript{42,11,22,23} Although not analyzed in the present study, it is assumed that if DGF were stratified by duration or severity, then at some point, depending also on the power of the study, an effect of DGF on DCD donor kidney graft outcome would be identified. Taken to an extreme, persistent DGF, also known as primary nonfunction has an obvious impact on graft survival. However, any degree of DGF may be important, because it increases resource utilization (need for dialysis) and may increase length of stay and patient morbidity.

In this study, there were 2 characteristics that significantly influenced the incidence of DGF in opposing ways: prolonged CIT and use of EISOR. Similar to other recent randomized studies, the overall rate of DGF in the present study was >50%.\textsuperscript{24,25} However, with CIT >30 hours, the rate of DGF in our study rose to >80%. Conversely, the use of EISOR during organ procurement was associated with a reduction in the rate of DGF to approximately 20%. Others have observed the deleterious effect of CIT on post-transplantation kidney function and the potential benefits of extracorporeal support.\textsuperscript{26-31} Magliocca and associates found that 2 (8%) of 24 kidneys from DCD donors managed with extracorporeal support exhibited DGF.\textsuperscript{26} In Taiwan, Lee and co-workers instituted extracorporeal support of donors because of historically long WITs due to a complex legal consent process. Of 8 kidneys procured with extracorporeal support, 2 (25%) had DGF.\textsuperscript{28} In our study, 4 (21%) of 19 kidneys from donors managed with extracorporeal support displayed DGF, compared with 60% of kidneys from non-EISOR donors (p = 0.002). Two of the kidneys that developed DGF in the setting of EISOR came from the same donor, and these case studies were previously reported as an example of “resuscitating” kidneys from an unstable DCD donor with multiple risk factors.\textsuperscript{42} However, the EISOR group had a short CIT because EISOR was performed only at the study site. A non-EISOR control group of 53 recipients of only local DCD kidneys with CIT <30 hours was selected to nullify the effect of CIT on other measurable effects related to the use of EISOR. Despite similar CITs, the local control group had a significantly higher rate of DGF than kidneys managed with EISOR, indicating that EISOR, and not other factors, produced a reduction in DGF. EISOR also resulted in significantly lower kidney resistance values on machine perfusion, a biologic effect that seems to corroborate the observed improvement in early graft function and a lower DGF rate. Others have found that such a difference in resistance values between 0.18 ± 0.05 mmHg/mL/min (seen with EISOR) and 0.25 ± 0.1 mmHg/mL/min (control group) is not just statistically significant, but also clinically significant.\textsuperscript{43,44} Use of EISOR and lower rates of DGF translated into a shorter length of initial hospital stay after DCD kidney transplantation: up to 3 days shorter on average. This decrease in resource utilization should help offset expenses associated with the use of EISOR and encourage its broader application. Use of EISOR was also associated with a trend toward improved graft survival and function, which might become significant with larger numbers and more experience.

In summary, a number of lessons were learned from this single-center retrospective study of DCD kidney transplantation. The optimal donor and recipient characteristics are a DCD ECD managed with EISOR with CIT <30 hours combined with a younger (<60 years old) recipient. Improved results with DCD ECD kidneys might be achieved as dual transplants, with the more liberal use of EISOR, by minimizing CIT, or in selecting younger recipients with a lower metabolic requirement. This study, along with previous observations by others, confirms that DGF and WIT, as currently defined, do not have the same deleterious effects after DCD as after donation after brain death kidney transplantation. Although the rate of DGF in DCD kidneys may be double that of donation after brain death kidneys, few DCD kidneys result in primary nonfunction and medium-term graft outcomes are very good. Finally, the use of EISOR had a clear beneficial impact on the initial function of DCD kidneys independent of WIT; it reduced the rate of DGF, and this clinical outcome was associated with a reduction in resistance values measured on machine perfusion. Use of EISOR was also associated with a significant reduction in length of initial hospital stay after kidney transplantation, an outcome that should encourage wider acceptance of its use.

**Author Contributions**

Study conception and design: Farney, Stratta
Acquisition of data: Hines, Farney, Stratta, al-Geizawi
Analysis and interpretation of data: Farney, Stratta, Rogers, al-Geizawi
Drafting of manuscript: Farney, Stratta
Critical revision: Farney, Stratta, Hines, al-Geizawi, Rogers

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Discussion

DR DEVIN ECKHOFF (Birmingham, AL): The lack of organ availability is probably the most pressing problem that we have in transplantation. It is conceptualized that potential organ recipients are waiting on the list, but in reality these individuals’ health is deteriorating and these people are dying. Whether it’s a liver transplant or a heart, this population will die without life-saving organ transplants. So it is imperative that we find better ways, or more organs, to transplant them. A classic illustration of this fact is the 5-year survival of an insulin-dependent diabetic on dialysis is only about 30%; this more than doubles after a renal transplant. Transplantation has been shown to improve quality of life and longevity, so it is essential that we get more organs to transplant into more people. So I commend you on your efforts at expanding the donor pool.

The first question I have for you is, because you clearly identify cold ischemia as being an important factor for adverse graft function, what measures are you undertaking to minimize cold ischemia time? Are you doing virtual crossmatches? Selecting recipients with low panel reactive antibodies? Or is the length of cold ischemia reflecting an institutional problem, ie, not having enough resources, such as operating room availability, to get the patients transplanted in a timely manner. The second question centers on recipients. We know from the liver experience of obtaining good outcomes using “marginal” donors, that it is important to not only pick good donors, but choosing the right recipients is equally important. What are you doing on the recipient side? Do you do anything special to prescreen the recipients that you select? I know you look at calculated glomerular filtration rate, but do you look at patients who may be able to tolerate the physiologic stress test of not getting an organ that works right away, a prolonged hospitalization? In the manuscript, you noted that your recipients who are older than 60 years old have a higher incidence of malignancy as well as death from infection. It appears that this group may be overimmunosuppressed, so have you modified your immunosuppressive protocol for this group of transplant recipients?

Last, I have more of an ethical or conceptual question. If we use all these donors that are within a hospital, we still won’t have enough donors to transplant all the patients on the waiting list. So what efforts do we, as a transplant community, need to take on the national level to get more donors? What is your opinion as far as first person consent and presumed consent as is used in a many models in Europe? Finally, it was just recently reported in the lay press about an effort being undertaken in New York, where they are going to have an organ donor team potentially go to a scene or home to try to help recover potential organ donors who die in the field and bring them to the hospital for organ donation. Is that too much too soon, or do you applaud those efforts?

DR PHILIP BOUDREAU (New Orleans, LA): Once again, Dr Stratta and his group are leading the charge in exploring the limits of how we can maximize the use of a scarce resource for transplantable organs. This study, like any good one, generates more questions than it answers, and I have several in 3 main areas. Clearly, there is more than one kind of ischemia, and more than one kind of delayed graft function, because delayed graft function in standard criteria, deceased brain-dead donors, leads to poor kidney graft outcomes, more rejection episodes, and worse long-term kidney functions. But those were not the findings in the case of the deceased cardiac death donors (DCD) as presented here. The agonal ischemia that results in delayed graft function must be a different kind of injury than the injury that results in delayed graft function from a standard brain-dead donor. Perhaps that might be the topic of another paper next year.

I would like to ask the authors why you suspect that delayed graft function did not adversely affect long-term and short-term outcomes, rejection episodes for these DCD transplants? Were the patients treated more expectantly because you were anticipating delayed graft function? Did you do something differently to treat these patients to minimize the adverse effects of potential rejection episodes or the extended use of steroids, for instance?

Second, although we had all hoped that machine perfusion would decrease our delayed graft function rates, it does not appear to be borne out. It could be that the information gained from machine perfusion, such as resistance characteristics and flow characteristics, allows us to make better choices in terms of selecting which kidneys we should use and which ones we should avoid.

And last, the idea of extracorporeal perfusion that can transform suboptimal organs into better performing ones has merit and should be further studied. It is hoped that the cost savings on the back end will mitigate the increased costs on the front end of performing the procedure. Regarding the extracorporeal support in DCD organ recovery, have you had occasion to precannulate for extracorporeal perfusion and then have the donor not arrest? And if that is the case, what do you do? As a corollary to that question, have you had instances of cardiac reanimation after placing the individual on extracorporeal circulation membrane oxygenation (ECMO)? And, if so, how have you modified your procedure?