Influence of Pulsatile Perfusion Preservation on Outcomes in Kidney Transplantation from Expanded Criteria Donors

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BACKGROUND: Expanded criteria donors (ECDs) increase the donor organ pool, but the value of transplanting these kidneys has been questioned because of concerns about diminished survival, poorer renal function, and higher rates of delayed graft function.

STUDY DESIGN: Retrospective analysis of intermediate-term outcomes in ECD kidney transplantations according to method of preservation at a single center using a standardized approach.

RESULTS: Over a 5-year period, we performed 141 donations-after-brain-death ECD kidney transplantations into adult recipients. A total of 114 kidneys (81%) were managed with combined cold-storage and pulsatile perfusion preservation (PPP), and the remaining 27 (19%) were preserved with cold storage (CS). The PPP group had a higher proportion of kidneys preserved for longer than 30 hours (28% versus 0, $p < 0.001$) and a longer mean cold ischemia time (24.5 hours PPP versus 19 hours CS, $p < 0.01$). Other donor and recipient characteristics were similar between groups. Incidence of delayed graft function was 11% in PPP-stored kidneys versus 37% in CS kidneys ($p = 0.002$). With a mean followup of 27 months, patient (91% PPP versus 96% CS) and kidney graft survival (81% PPP versus 81.5% CS) rates were comparable. Mean 12-month serum creatinine (1.9 mg/dL) and calculated Modification of Diet in Renal Disease glomerular filtration rate (41 mL/min) values were similar between groups.

CONCLUSIONS: Despite longer cold ischemia times, recipients of ECD kidneys managed with PPP had similar survival and functional outcomes, but experienced a marked reduction in the rate of delayed graft function. (J Am Coll Surg 2007;204:873–884. © 2007 by the American College of Surgeons)

Kidney transplantation remains the treatment of choice for many patients with end-stage renal disease and is a superior longterm therapy compared with dialysis, in terms of quality of life and life expectancy.[1] Because of improving transplantation outcomes, donor and recipient selection criteria are evolving. Unfortunately, the waiting list continues to grow disproportionate to the number of donor organs available for transplantation. Since November 2006, the United Network for Organ Sharing (UNOS) national waiting list exceeded 100,000 candidates, of which over 70,000 were awaiting kidney transplants.[2] Median waiting times for kidney transplant in the US exceed 3 years in the absence of a living donor.[2] For some patients, the waiting list has become a false promise, as 6% of patients on the kidney waiting list (10% of diabetic patients) die each year awaiting a potential life-enhancing and life-prolonging transplantation.[2]

The increasing disparity between organ supply and demand challenges the transplantation community to maximize and optimize the use of organs from all consented donors. Recent increases in kidneys from deceased donors (DDs) have been predominantly a result of increasing use of older donors, donation-after-cardiac-death (DCD) donors, and DDs with other characteristics that might be associated with increased risk of graft dysfunction.[2,3] To counteract the escalating discrepancy between organ availability and need, UNOS initiated policy in 2002 defining

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Abbreviations and Acronyms

BMI = body mass index
CIT = cold ischemic time
CMV = cytomegalovirus
CrCl = creatinine clearance
CS = cold-storage preservation
DCD = donation after cardiac death
DD = deceased donor
DGF = delayed graft function
DKT = dual-kidney transplantation
ECD = expanded criteria donor
GFR = glomerular filtration rate
PPP = pulsatile perfusion preservation
PRA = panel reactive antibody
PVN = polyomavirus-induced nephropathy
rATG = rabbit antithymocyte globulin
SCr = serum creatinine
TAC = tacrolimus
UNOS = United Network for Organ Sharing

and providing guidelines for use of expanded criteria donor (ECD) kidneys.[3-5] ECD kidneys can be associated with declining renal function, limited nephron reserve, and have an inherent reduced graft viability, resulting in a relative risk of graft loss of 1.7 when compared with kidneys from younger donors.[3-5] Growing acceptance and use of ECD kidneys has been tempered by data suggesting that these kidneys have an increased susceptibility to ischemia-reperfusion injury, leading to higher rates of primary nonfunction; delayed graft function (DGF) and acute rejection.[3-7] These concerns have fueled initiatives to qualitatively assess these kidneys before transplantation by use of ex vivo biopsies and machine preservation technology.[8-10]

It is well-established that DGF is a risk factor not only for graft dysfunction, acute rejection, and poorer intermediate-term graft survival, but is also directly related to DD category.[2,11,12] According to UNOS data, the incidence of DGF is highest with DCD kidneys (44%), intermediate with ECD kidneys (33%), and lowest with standard-criteria donor kidneys (21%).[2,11,12] Once a DD kidney is recovered, there are two methods of preservation: simple cold hypothermic storage (CS) and pulsatile perfusion preservation (PPP).[9,10,13-15] CS preservation relies on customized solutions that contain specialized additives, such as impermeants, buffers, antioxidants, and energy precursors to counteract cell swelling and minimize apoptosis.[16] In contrast, PPP involves an ex vivo, hypothermic pulsatile perfusion machine that delivers oxygen and nutrients through a specialized preservation solution to the kidney and removes waste products in an attempt to mimic circulation, thereby preserving endothelial and parenchymal integrity and reducing vasospasm.[13-15]

There have been numerous previous studies directly comparing CS with PPP, particularly with standard-criteria donor kidneys, suggesting that neither preservation technique was associated with a clinical advantage.[13-15,17,18] Two recent registry-based studies analyzing use of PPP in ECD kidneys have reported an improvement in use, and lower rates of DGF, associated with this method of preservation.[9,10] The purpose of this study was to compare intermediate-term outcomes in adult recipients of ECD kidney transplants according to method of preservation at a single center using a standardized management approach.

METHODS

Study design

We conducted a retrospective chart review of all donations-after-brain-death ECD kidney transplantations performed in adult recipients at our center from November 1, 2001 to November 18, 2006 (minimum 1-month followup). Specific exclusions included pediatric recipients (younger than 20 years of age); simultaneous kidney-pancreas transplant recipients; and DCD, standard-criteria donor, and living-donor kidney recipients. A total of 141 ECD kidney transplantations met the entry criteria and were categorized according to method of preservation (CS versus PPP). Because nearly all kidneys that were placed on the pulsatile perfusion apparatus had variable periods of CS preservation, either before or after pumping, for study purposes the PPP group will be referred to as combined CS and PPP.

Definitions

ECDs were classified by UNOS definition as all DDs older than 60 years of age and DDs 50 to 59 years of age with any two of the following criteria: history of hypertension; cerebrovascular cause of brain death; or terminal serum creatinine (SCr) level $>$ 1.5 mg/dL.[3-6] For purposes of this study, any DD not meeting these ECD criteria was defined as a standard-criteria donor. Donor and recipient characteristics and outcomes were stratified according to method of preservation. DGF was defined as the need for dialysis in the first week posttransplantation. Renal allograft loss was defined as death with a functioning graft, allograft nephrectomy, resumption of dialysis, retransplantation, or return to pretransplantation SCr level.

Donor evaluation and management

No specific DD upper age limit was excluded from consideration, and this series included 22 transplantations from DDs 70 years of age or older (oldest 78 years). The Cockcroft-Gault formula was used to estimate donor cre-

atinine clearance (CrCl), using either ideal or adjusted body weight (in donors > 30% ideal body weight) to calculate projected donor kidney function and to determine single or dual-kidney transplantation (DKT) into a single recipient.[19,20] If the estimated donor CrCl was > 65 mL/min, then a single-kidney transplantation was performed, preferably into an older recipient with a body mass index (BMI; calculated as kg/m^2) < 25. If estimated CrCl was < 40 mL/min, then the kidney(s) were not usually transplanted at our center. If the estimated CrCl was 40 to 65 mL/min, then a bilateral DKT was typically performed using a lower midline IP or extraperitoneal approach.[19] In general, if the terminal SCr was > 2.0 mg/dL or the donor SCr was rising, then the kidney(s) were not used. In this series, 14 DDs had a calculated CrCl ≤ 50 mL/min, with the lowest being 36 mL/min.

Ex vivo assessment

Donor-kidney biopsy was also used to assist in the evaluation of preexisting and terminal parenchymal pathology. A donor-kidney biopsy showing > 40% glomerulosclerosis or moderate to severe tubular, interstitial, or vascular changes was a contraindication to kidney use.[8,20,21] Whenever possible, ECD kidneys were placed on PPP to minimize preservation injury, maintain functional reserve, and provide another means of assessment.[22] Within our organ procurement organization, locally procured kidneys are routinely placed on the perfusion pump at the accepting center's discretion or, if the DD is older than 40 years, is hemodynamically unstable or oliguric, has a SCr > 1.2 mg/dL, or has a history of hypertension or diabetes. ECD or DCD donor kidneys are routinely pumped, and imported kidneys meeting these criteria are also pumped if time permits.

PPP was performed using a standardized, dual-kidney perfusion system (RM3 Renal Preservation System, Waters Medical Systems). Kidneys were perfused with Belzer's hypothermic machine preservation solution (KPS-1, Organ Recovery Systems, Inc) at 5°C at an initial pressure of 50 mmHg (rarely 55 to 60 mmHg if history of severe hypertension in donor).[23] Routine additives to the system included penicillin (250,000 U), insulin (40 U), dexamethasone (16 mg), and mannitol (3 g). Additional treatment interventions were based on measurements of flow, pressure, and resistance in the circuit and included chemical resuscitative measures, such as administration of additional mannitol (1 g) and vasodilators such as verapamil (10 mg, maximum three doses), papaverine (10 mg, maximum three doses), and phentolamine (5 mg, maximum three doses) to maintain a flow > 100 mL/min and a resistance < 0.30 mmHg. Although pump parameters were not exclusively used to discard kidneys, a flow rate > 80 mL/min and a resistance < 0.50 mmHg after a minimum of 6 hours on the PPP apparatus were considered thresholds for use.[22] If the kidney(s) were pumping well, cold ischemic times (CIT) in excess of 40 hours were considered acceptable.

Recipient selection

At our center, no specific upper age limit is an absolute contraindication to kidney transplantation, and this series included 16 recipients 70 years of age or older (oldest was 81 years). All patients undergo a comprehensive pretransplantation medical, psychosocial, and financial evaluation, with emphasis placed on the cardiovascular system and any other nonrenal organ failure to determine operative risks and physiologic age.[20] Patients approved for transplantation are assigned a risk assessment (to aid in waiting list maintenance and followup), and a decision is made whether or not to list the patient as willing to accept an ECD kidney. In general, if the patient is younger than 40 years of age, highly sensitized (panel reactive antibody [PRA] level > 50%), morbidly obese (BMI > 30), or a retransplantation candidate, then it is recommended that the patient not be listed as willing to accept an ECD kidney. At the time of transplantation, patients are selected on the basis of blood-type compatibility, waiting time, HLA-matching, a negative flow cytometry T- and B-cell crossmatch, and special listing for ECD in accordance with UNOS guidelines.[20] Listing patients for an ECD kidney neither mandates nor restricts them to receiving an ECD kidney, as the decision to accept any kidney, whether from an ECD or standard criteria donor, is reaffirmed at the time of the offer with informed consent.

Whenever possible, ECD kidneys are used by matching estimated renal functional mass to recipient nephron need, including use of DKTs (n = 16).[19,20] Recipients of DKTs are typically younger than 60 years of age because of the greater anesthetic and surgical risks associated with this longer procedure. Recipient selection for ECD kidneys is based on identifying low immunologic risk and low metabolic need patients such as primary transplant, recipient age older than 40 years, HLA-matching, low PRA (usually 0%), BMI < 25, and informed consent for either single or DKT.[20]

Immunosuppression

All ECD kidney transplantation patients received depleting antibody induction with either rabbit antithymocyte globulin (rATG, Thymoglobulin, Genzyme Corp) at a dose of 1.5 mg/kg (maximum dose, 150 mg) based on actual body weight (n = 104) or alemtuzumab (Campath-1H, Millennium Pharmaceuticals) 30 mg IV as a single intraoperative dose (n = 37).[20] The first dose

of rATG was given intraoperatively and subsequent rATG infusions were administered at alternate-day intervals for a minimum of three and a maximum of seven doses, depending on initial graft function. Maintenance immunosuppression consisted of tacrolimus (TAC), mycophenolate mofetil, and tapering doses of steroids. Administration of TAC was delayed until the patient had exhibited a brisk diuresis and a declining SCr level (< 4.0 mg/dL). Target 12 hours TAC trough levels were based on donor quality and recipient immunologic risk, but typically ranged from 6 to 10 ng/mL for ECD kidney recipients. In patients older than 60 years, the maximum mycophenolate mofetil dose was kept at 500 mg twice daily. In the last 2 years, 45 low−immunologic risk ECD patients have successfully undergone early steroid elimination. Details about our immunosuppressive regimen have been published previously.[20]

Anti-infective prophylaxis

All patients received surgical-site prophylaxis with a first-generation cephalosporin for 24 hours, antifungal prophylaxis with nystatin for 1 to 2 months, and anti-*Pneumocystis* prophylaxis with sulfamethoxazole or trimethoprim (dapsone if allergic to sulfa) for 12 months. Antiviral prophylaxis consisted of oral valganciclovir for 3 to 6 months, depending on donor and recipient cytomegalovirus (CMV) serologic status. Specifics about drug dosing and duration have been published previously.[20]

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 blood pressure $< 140/90$ mmHg, fasting serum cholesterol < 200 mg/dL, hematocrit $> 30\%$, and fasting blood glucose < 126 mg/dL. Diagnosis of renal allograft rejection was suggested by an unexplained rise in SCr level of > 0.3 mg/dL or a 25% increase from baseline level and confirmed by ultrasonography-guided percutaneous biopsy. Grade I rejection episodes were treated with three steroid boluses or an oral prednisone recycle. Grade I rejection episodes without biochemical evidence of improvement or unresolved infiltrates on a repeat biopsy within 2 to 3 weeks (persistent or steroid-resistant rejection) were treated with rATG rescue therapy. Grade II and III rejection episodes were also treated with rATG for five to seven doses, depending on biochemical and clinical response.[20]

CMV infection was defined as positive blood cultures (early antigen) or polymerase chain reaction assay. Treatment of CMV infection consisted of IV ganciclovir or oral valganciclovir for 2 to 4 weeks and selective use of CMV hyperimmune globulin (CytoGam, MedImmune, Inc) concomitant with a reduction in immunosuppression.[20] Polyomavirus-induced nephropathy (PVN) was diagnosed on the basis of renal allograft biopsy and treated with a reduction in immunosuppression and conversion from mycophenolate mofetil to leflunomide. Surveillance monitoring of urine cytology for decoy cells, blood polymerase chain reaction for polyomavirus or CMV, and kidney transplant biopsies were not performed unless clinically indicated.

Posttransplantation renal allograft function was evaluated by measuring SCr levels and calculating glomerular filtration rate (GFR) using the abbreviated Modification of Diet in Renal Disease formula.[24]

Statistical analysis

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. Univariate analysis was performed by unpaired *t*-test for continuous variables, chi-square test for categorical variables, and Fisher's exact test when data were sparse. Unadjusted actual patient and graft survival rates were reported. Actuarial patient and graft survival curves were also computed using Kaplan-Meier method and compared using log-rank test. Categorical data were summarized as proportions and percentages and continuous data were summarized as means and standard deviations. A two-tailed p value of < 0.05 was considered to be significant.

RESULTS

Over a 5-year period, we performed a total of 373 DD kidney transplants into adult recipients, including 203 (54%) from standard-criteria donor, 141 (38%) from ECD, and 29 (8%) from DCD donors. The majority of ECD kidneys were refused by multiple other transplantation centers, and many were targeted for discard. ECD kidneys were used by matching estimated renal functional mass to recipient metabolic need, including use of DKTs ($n = 16$) exclusively into recipients younger than 60 years of age.

Donor, recipient, and transplant characteristics according to method of preservation are shown in Table 1. Not surprisingly, there were no marked differences in donor characteristics, as both groups had a mean donor age younger than 60 years and similar proportions of donors older than 70 years of age. The majority of donors in both groups sustained brain death from cerebrovascular causes and had a history of hypertension. Although differences in terminal donor SCr levels approached significance, esti-

Table 1. Donor, Recipient, and Transplant Characteristics

Characteristics	CS/PPP (n = 114)	CS (n = 27)	p Value
Donor age (y)	61.6 ± 6.8	60.5 ± 6.6	NS
Donor BMI*	28.0 ± 5.9	30.1 ± 7.2	0.14
Brain death: cerebrovascular, n (%)	80 (70)	16 (59)	NS
History of donor hypertension, n (%)	77 (68)	16 (59)	NS
Donor age > 70 y, n (%)	19 (17)	3 (11)	NS
Estimated CrCl (mL/min)	73.5 ± 20	70.9 ± 22	NS
Preretrieval SCr (mg/dL)	1.04 ± 0.3	1.18 ± 0.5	0.08
Cold ischemia time (h)	24.5 ± 8.1	19.0 ± 5.7	0.0014
CIT > 30 h, n (%)	32 (28)	0	<0.001
HLA-mismatch	1.8 ± 1.4	2.15 ± 1.8	NS
0-antigen mismatch, n (%)	10 (10)	7 (26)	0.02
0% PRA, n (%)	96 (81)	24 (89)	NS
PRA > 40%, n (%)	12 (11)	0	0.12
Dual-kidney transplant, n (%)	14 (12)	2 (7)	NS
Recipient age	55.4 ± 11	60.1 ± 9.6	0.047
Recipient BMI*	24.1 ± 4.1	24.8 ± 4.1	NS
Recipient gender male, n (%)	54 (47)	16 (59)	NS
Waiting time (mo)	21 ± 20	21 ± 17	NS
Recipient African-American, n (%)	45 (39)	6 (22)	0.12
Recipient with diabetes, n (%)	32 (28)	7 (26)	NS
Retransplant, n (%)	7 (6)	1 (4)	NS

Data are presented as mean ± SD, except where indicated.
*Calculated as kg/m^2.
BMI, body mass index; CIT, cold ischemia time; CrCl, creatinine clearance; CS, cold-storage preservation; PPP, pulsatile perfusion preservation; PRA, panel reactive antibody; SCr, serum creatinine.

mated mean donor CrCl values (72 mL/min) were similar in both groups because of slight differences in donor BMIs in the two groups. Kidneys preserved with combined CS and PPP had considerably longer CITs by a mean of 5.5 hours. All kidneys preserved for longer than 30 hours (n = 32) were in the CS and PPP group, with CITs extending up to 47 hours.

The CS group had a higher proportion of 0-antigen mismatched kidney transplants, although the mean HLA match was not notably different between groups. Both groups were comprised predominantly of low−immunologic risk patients (low PRA levels, few retransplantations), but the 12 recipients with PRA levels > 40% were exclusively in the CS and PPP group. Kidney transplant recipients in the CS group were older by a mean of 4.6 years and other demographic (gender, diabetes as cause of end-stage renal disease) and transplant characteristics were similar between groups, including waiting time and proportion of DKTs. The CS and PPP group had a slightly higher proportion of African-American recipients (39% CS and PPP versus 22% CS, p = 0.12).

Outcomes are shown in Table 2. A total of 108 patients (77%) had at least 1-year followup. Actual patient (91% CS and PPP versus 96% CS) and kidney graft (81% CS and PPP versus 81.5% CS) survival rates were similar between groups, with a mean followup of 27 months. Four-year actuarial patient (Fig. 1) and kidney graft (Fig. 2) survival rates were also similar. There were a total of 11 deaths in the study, including 10 (9%) in the CS and PPP and 1 (4%) in the CS groups (p = NS). Four patients died

Table 2. Outcomes According to Method of Preservation

Outcomes	CS/PPP (n = 114)	CS (n = 27)	p Value
Actual patient survival, n (%)	104 (91)	26 (96)	NS
Actual graft survival, n (%)	92 (81)	22 (81.5)	NS
Delayed graft function, n (%)	12 (11)	10 (37)	0.002
Followup (mo)	26 ± 18	31 ± 15	NS
Primary nonfunction, n (%)	3 (3)	1 (4)	NS
Acute rejection, n (%)	14 (12)	4 (15)	NS
CMV infection, n (%)	7 (6)	3 (11)	0.40
Polyomavirus infection, n (%)	4 (4)	3 (11)	0.13
CMV + PV infections, n (%)	11 (10)	6 (22)	0.097
Initial length of stay (d)	8.2 ± 6.8	8.5 ± 5.3	NS
1-year SCr (mg/dL)	1.9 ± 1.0	2.0 ± 1.7	NS
1-year MDRD GFR (mL/min)	42 ± 14	41 ± 10	NS

Data are presented as mean ± SD, except where indicated.
CMV, cytomegalovirus; CS, cold-storage preservation; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; PPP, pulsatile perfusion preservation; PV, polyomavirus; SCr, serum creatinine.

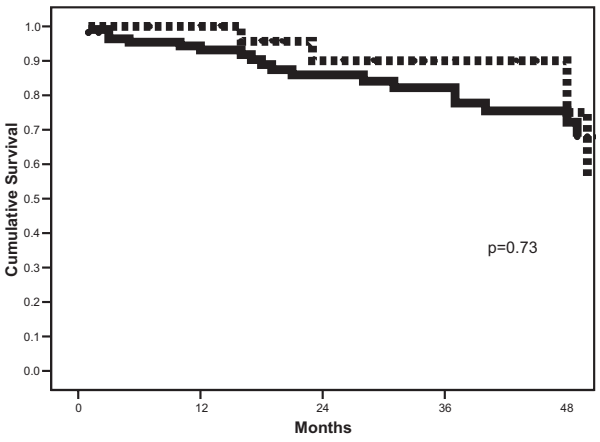

Figure 1. Four-year actuarial patient survival rates in cold-storage preservation (CS)/pulsatile perfusion preservation (PPP) versus CS expanded criteria donor kidney transplant recipients. Dotted line, CS; solid line, CS-PPP.

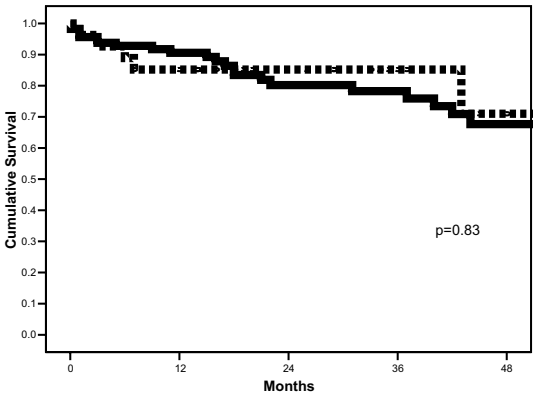

Figure 2. Four-year actuarial kidney graft survival rates in cold-storage preservation (CS)/pulsatile perfusion preservation (PPP) versus CS expanded criteria donor kidney transplant recipients. Dotted line, CS; solid line, CS-PPP.

within 3 months of transplantation, all in the CS and PPP group; only one of these early deaths was related to poor graft function. The remaining seven late deaths occurred at a mean of 29 months; six patients experienced death with a functioning graft and only one late death was directly transplant-related (fungal infection). A total of 27 kidney grafts were lost, including 22 (19%) in the CS and PPP and 5 (18.5%) in the CS groups (p = NS). There were nine early graft losses within 3 months of transplantation, including seven (6%) in the CS and PPP group compared with two (7%) in the CS group. There were six immediate (within 1 week) graft losses, including five (4%) in the CS and PPP group (two PNF, two thromboses, one death with a functioning graft) and one (4%) in the CS group (PNF). The remaining 18 late-graft losses occurred at a mean of 22 months after transplantation (6 deaths with a functioning graft, 5 chronic allograft nephropathy, 2 PVN, 2 acute and chronic rejection, 2 recurrent glomerular disease, and 1 renal artery stenosis with late thrombosis) and no major differences were noted between groups.

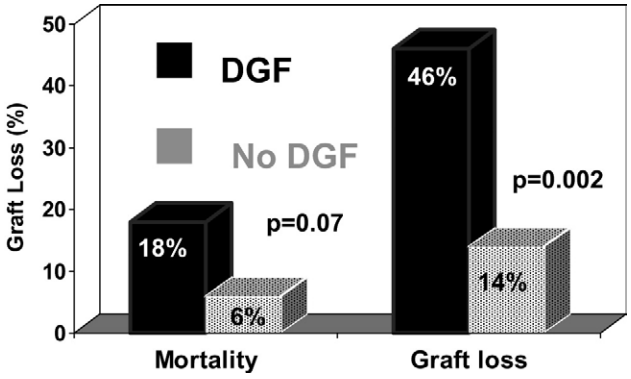

Figure 3. Mortality and graft loss according to presence or absence of delayed graft function (DGF) in all expanded criteria donor kidney transplant recipients.

Preserving ECD kidneys by CS and PPP lowered the rate of DGF from 37% to 11% (p = 0.002). In the 32 patients in the CS and PPP group with CITs longer than 30 hours, the incidence of DGF was 12.5%. In the 22 patients with DGF, the mean CIT was 22.7 hours, which was similar to the mean CIT for patients without DGF. In both groups combined, presence of DGF was not a major risk factor for subsequent acute rejection (18% incidence of acute rejection with versus 12% without DGF, p = NS). DGF was a risk factor for graft loss (46% incidence of graft loss in patients with DGF versus 14% without, p = 0.002; Fig. 3). The influence of DGF on patient survival approached but did not achieve significance (18% mortality in patients with DGF versus 6% without, p = 0.07; Fig. 3). Incidence of PNF, acute rejection, operative complications, and major infections were similar in both groups (Table 2).

Length of initial hospital stay, readmissions, and resource use were comparable between groups (p = NS). Incidence of viral infections (CMV, PVN) was twice as high in the CS group (22%) compared with the CS and PPP group (10%, p = 0.097). Of the 10 CMV infections, 6 occurred in patients with primary CMV exposure and only 1 in a patient with DGF. Of the seven cases of PVN, two (one in each group) resulted in graft loss. PVN developed in only one patient with DGF (4.5% in patients with versus 5% in patients without DGF). There were three cases of Epstein-Barr virus–associated posttransplantation lymphoproliferative disease, all in the CS and PPP group.

The incidence of DGF was slightly higher in African-American recipients in both groups separately and combined (overall 23% incidence of DGF in African-American versus 11% in non–African-American patients, p = 0.09),

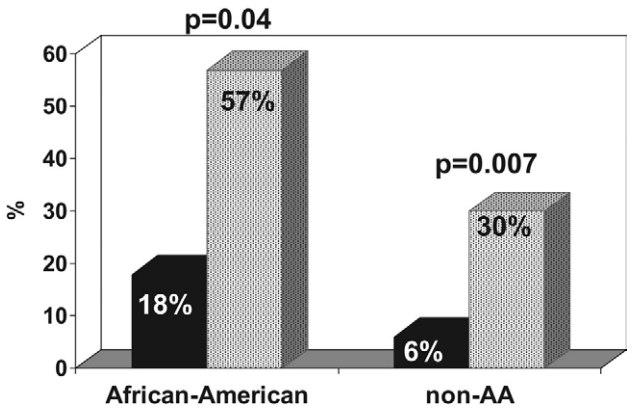

Figure 4. Incidence of delayed graft function in African-American (AA) and non−African-American expanded criteria donor kidney recipients according to method of preservation. Black bar, cold-storage preservation (CS)/pulsatile perfusion preservation (PPP); gray bar, CS.

but the magnitude of this effect was less pronounced in the CS and PPP kidney recipients (18% rate of DGF in African-American versus 6% in non−African-American patients, p = 0.06). Pumping kidneys reduced the rate of DGF in African-American recipients from 57% to 18% (p = 0.04), and reduced the rate of DGF in non−African-American recipients from 30% to 6% (p = 0.007, Fig. 4). Although the rate of kidney graft loss was slightly higher in African-American recipients in the CS group (33% African American versus 14% non-African American, p = 0.30), it was no different in the CS and PPP group (20% African American versus 19% non-African American, p = NS).

Both groups initially stabilized renal function at approximately 60% of the estimated donor CrCl, so that mean 12-month SCr levels (1.9 to 2.0 mg/dL) and Modification of Diet in Renal Disease−calculated GFRs (41 to 42 mL/min) were similar in both groups (Table 2).

DISCUSSION

ECDs aged older than 60 years and those aged 50 to 59 years with additional risk factors accounted for 177 kidney transplantations nationally in 1988 and > 1,400 in 2005.[2,3] At present, ECDs comprise approximately 20% of all DD kidneys in the US. The value of transplanting ECD kidneys has been questioned because there are data to suggest that these kidneys have a higher rate of primary nonfunction, DGF, acute rejection, and a greater susceptibility to preservation injury, drug toxicity, and posttransplantation hypertension.[3-10,25] In addition, ECD kidneys appear to be more resource-intensive, costly, and not appropriate for retransplantation.[7,26-28] The longevity of an ECD kidney is believed to be much shorter, with the half-life estimated to be 6 to 8 years, compared with 10 to 12 years with a standard criteria donor kidney from a DD.[3-8,29] Unfortunately, the loss of quality and quantity of life by those on the waiting list remains a sobering and staggering reality. Initial survival data suggest that receiving any kidney is a better treatment option than remaining on the waiting list, despite the fact that a spectrum of quality exists among the various DD categories.[25,29,30]

In October 2002, UNOS introduced new policy that not only defined but addressed special allocation issues pertaining to ECDs.[3-6] The UNOS guidelines were based on the principle of improving access to transplantation for patients whose life expectancy was less than their predicted waiting time for a kidney. Part of the intent of the UNOS policy was to minimize cold ischemia for ECD kidneys by preselecting patients most likely to benefit from them. The optimal use of ECD kidneys remains ill-defined because CITs remain excessive and the organ discard rate has not changed appreciably because of implementation of the ECD policy.[2,3,31]

The presence of DGF is an early marker of organ quality and preservation. DGF is a form of acute renal failure after kidney transplantation that results in oliguria, enhanced allograft antigenicity, and decreased longterm graft survival.[11,12] It represents a combined response to a series of ischemic, reperfusion, inflammatory, and immunologic injuries. The incidence of DGF has not changed appreciably in the last decade and typically occurs in 20% to 30% of donation-after-brain-death DD kidney transplantations.[2,11] The incidence is highest in DCD, intermediate in ECD, lower in standard-criteria donor, and lowest in living-donor kidney transplant recipients. Other risk factors for DGF include donor, procurement, preservation, transplant, and recipient issues. Each of these areas represents a potential opportunity for minimizing, preventing, or reversing the manifestations of ischemia-reperfusion injury. ECD kidneys are uniquely susceptible to ischemia-reperfusion injury because of older donor age, comorbidities such as hypertension and vascular disease, and the terminal effects of brain death on kidneys with limited functional reserve.[3-6,8-12] Older or ECD kidneys have decreased renal blood flow and intrinsic GFR, are accompanied by a number of histopathologic changes associated with senescence, and lose the ability to undergo compensatory hypertrophy.[6-8,21,25,31]

The presence of DGF doubles the rate of graft loss at 5 years after kidney transplantation compared with recipients with immediate graft function.[11] This is associated with a reduction in graft half-life from 11.5 to 7.2 years, which is eerily similar to the difference in graft half-life between recipients of standard-criteria donor and ECD kidneys.[3-8] In addition, DGF increases the risk of acute and

chronic rejection such that the presence of DGF and acute rejection reduces graft half-lives to 9.4 and 6.2 years for patients with immediate and DGF, respectively.[11,12] DGF increases length of initial hospital stay, initial hospital charges, is more resource-intensive, and has adverse psychologic and medical effects on the patient.[11,12] Consequently, efforts directed at minimizing DGF can be expected to have a number of beneficial effects.

The major risk factors for DGF appear to be warm and cold ischemia, which account for the hierarchy of DGF among the various donor categories.[11,12] Warm ischemia is more deleterious to initial organ function than cold ischemia, and the warm ischemia inherent in DCD kidneys accounts for the high rate of DGF within this DD category. For patients receiving kidneys from DCDs or ECDs, or both, the rate of DGF is $> 50\%$.[2] For patients receiving kidneys from donors with acute renal failure, DGF rates can approach 90%.[32] With regard to cold ischemia, it is estimated that after 12 hours of CS preservation, the rate of DGF increases by 5% for each 6 additional hours of cold ischemia.[11,12] Consequently, after 24 hours of cold ischemia, the rate of DGF is doubled compared with 12 hours of CIT.

PPP was initially developed in the 1960s by Belzer and colleagues[33] as a more physiologic method of renal preservation. In the 1980s, with the introduction of a new hypothermic machine preservation solution, PPP was touted as a superior method of organ preservation and CITs were extended to 30 to 40 hours and beyond without compromise in graft outcomes and attended by remarkably low rates of DGF ($< 10\%$).[23] Despite initial enthusiasm, prospective trials failed to demonstrate a substantial advantage in clinical outcomes for kidneys preserved in CS compared with PPP, particularly for standard-criteria donor kidneys with CITs of 24 hours or less.[13-18]

Although the added cost and complexity of PPP does not appear to justify its routine use for ideal kidneys with conventional CITs, a resurgence of interest has occurred in PPP as the preferred method of preservation for DCD and ECD kidneys.[9,10,22,34] In addition to reducing ischemic injury in kidneys that might have an enhanced susceptibility to injury during preservation, PPP also provides a quantitative assessment of renal vasospasm (and terminal ischemic injury) by nature of the pump parameters that are generated during machine preservation. These pump numbers can have prognostic importance for the ultimate viability of the kidney, which might influence the decision about use or discard.[22] It is surprising that, despite increasing numbers of DCD and ECDs nationally, the annual proportion of DD kidneys preserved by PPP has increased only modestly from 15% to 22% in the last decade.[2] In 2006, the proportion of kidneys preserved with PPP is directly related to donor category (DCD 57%, ECD 28%, standard criteria donor 14%, overall DD 21%).[2]

Our management protocol for the ECD kidney was based on a number of potential nephron-sparing maneuvers, including attempts to minimize CIT (that were largely unsuccessful), PPP whenever logistically possible, front-loaded immunosuppression with depleting antibody induction to minimize preservation injury and acute rejection, delayed administration of a calcineurin inhibitor, and targeting lower TAC levels longterm to minimize drug toxicity.[20] Because many of the ECD recipients were profiled based on low−immunologic risk and had a negative flow cytometry T- and B-cell crossmatch, we were comfortable targeting lower TAC levels to achieve a balance between efficacy and toxicity.

In this study, ECDs were performed at our center at nearly twice the national rate, and PPP was used at nearly three times the national rate for ECD kidneys. Implementation of the UNOS policy had no discernible effect on minimizing CIT, which was considerably greater in the CS and PPP group and reflects the fact that many of the kidneys in both groups (CS and PPP and CS) were imported from other organ procurement organizations. All of the ECD kidneys with CITs longer than 30 hours were in the CS and PPP group. In addition, all of the sensitized patients, a larger proportion of African-American recipients, and fewer 0-antigen mismatched kidneys were in the CS and PPP group. Despite these apparent drawbacks, use of CS and PPP in ECD kidneys remarkably led to a marked reduction in the rate of DGF compared with CS preservation. It is interesting to note that the cited national incidence of DGF with ECD kidneys is 33%, which is similar to our rate of DGF (37%) in ECD kidneys that were not preserved by PPP.

Presence of DGF was associated with a higher rate of graft loss in both groups. Nearly 40% of recipients in the CS and PPP group were African American. We analyzed a number of established risk factors known to adversely influence kidney graft survival rates, such as ethnicity, DGF, and acute rejection in both groups. Although similar risk factors for graft loss were present in both groups, the magnitudes of the effects were blunted in the CS and PPP group. For example, although African-American recipients had higher rates of DGF, acute rejection, and graft loss compared with non−African-American recipients, transplanting an ECD kidney into an African-American recipient under the umbrella of CS and PPP appeared to confer improved outcomes when compared with an ECD kidney transplanted into an African-American recipient with CS preservation.

A number of clinical outcomes and parameters of morbidity and resource use were similar between groups. We did not note an increased risk of acute rejection in the CS group, despite a higher rate of DGF. Intermediate-term patient and graft survival rates and renal function were likewise similar. Interestingly, one effect that was observed in our study was a somewhat greater propensity ($p = 0.097$) for viral infections (CMV or PVN) in the CS group. Previous studies have suggested that pumping kidneys might reduce viral load or risk of disease transmission.[35] In addition, it is tempting to speculate that CS and PPP kidneys, by nature of having less cellular injury and reduced DGF, might be less susceptible to subsequent viral activation and infection.

In summary, the critical organ shortage poses a formidable challenge to maximize use and optimize function of all recovered kidneys.[36,37] Prevention of DGF can have beneficial short- and longterm consequences, and the results of this study, similar to previous registry analyses, clearly demonstrate that use of PPP can reduce the incidence of DGF in ECD kidney transplantation.[9,10] In addition, PPP provides an ex vivo assessment of marginal donor kidneys and can rescue some kidneys that were doomed to either failure or nonuse. Based on the findings of this study, we believe that ECD kidneys should be routinely managed with PPP to improve outcomes, promote sharing, safely extend CIT when necessary, and reduce organ discard. Ultimately, understanding the factors that determine outcomes and longer-term followup are necessary to fully delineate the benefits and risks of various management strategies in ECD kidney transplantation.

Author Contributions

Study conception and design: Stratta, Moore, Farney, Rogers
Acquisition of data: Moore, Gautreaux, Iskandar
Analysis and interpretation of data: Stratta, Farney, Rogers, Hartmann, Reeves-Daniel, Adams
Drafting of manuscript: Stratta, Moore, Farney
Critical revision: Stratta, Gautreaux, Iskandar, Adams

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Discussion

MARK H DEIERHOI, MD (Birmingham, AL): The constant litany in transplantation over the past 15 to 20 years has been the organ shortage and the fact that there are enormously greater numbers of patients waiting for kidneys than there are kidneys available. This has become even more of an issue as national data on survival of patients with transplants and survival of patients on dialysis are now being compared, demonstrating that for every patient group that has been looked at, survival is better with a transplant. So kidney transplants extend life for the vast majority of patients.

The response to this, nationally, has been various efforts to increase the number of donors. And one way the country has focused on this has been to look at donors for whom outcomes are slightly lower, particularly the expanded criteria donors. It has been demonstrated that with expanded criteria donors, just as for standard donors, patients' lives are in fact extended by the transplant and there is significant benefit as well in patients' quality of life. So it is clear that in general, expanded criteria donors are worthwhile.

But there is significant risk to the use of these donors and there is a downside to using kidneys that are potentially less viable and have higher rates of delayed graft function and lower longterm survival. We know that delayed graft function does appear to increase the risk of patient mortality. It almost certainly has an impact on graft survival. We know from our own data at our institution that the reality of transplantation for most patients is that they will get one shot at a transplant.

Because of comorbidities, factors related to patients getting older, and sensitization, the vast majority of patients will get one opportunity to get a transplant. So a failed graft, for any patient, and particularly if it fails early, can be a disaster and may mean a life of dialysis.

We have two real questions to deal with on the expanded criteria donors; and those are, how do we decide which kidneys actually can be used safely and are there criteria that we can use to identify expanded criteria donors whose kidneys will not benefit patients; and, are their ways to improve the function of these organs to increase the percentage that is actually used?

Dr Stratta's group has made a number of significant contributions in defining the criteria for using expanded criteria donors, and this paper is no exception. Here they have looked at the benefits of pulsatile preservation to determine if, in fact, there is some benefit to these patients by using pulsatile preservation as opposed to the cold storage, which is the standard kidney preservation in most of the country. They demonstrate that in terms of delayed graft function there appears to be a significant benefit. This does not, at least in their series, translate into increased graft survival, but there does appear to be a significant downside to delayed graft function in terms of patient mortality.

Based on their data, I do have a number of questions about their information and about their management of expanded criteria donors. First, I would like to know what percentage of kidneys placed on pulsatile perfusion were discarded subsequently as a result of their analysis of those kidneys either by biopsy or perfusion parameters.

Was there a difference between kidneys that were retrieved by their organ procurement agency and imported kidneys in the proportion of time that the kidneys spent on pulsatile perfusion, and did the percentage of time in pulsatile perfusion have any impact on either delayed graft function or outcome for those transplants?