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Expanding the Donor Pool: Effect on Graft Outcome

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The short-term success rate of cadaveric renal transplants has improved dramatically during the past decade. In 1990, one-year graft survival rates were about 70%; by 2000, they were greater than 90% (United States Renal Data System, 2001). Unfortunately, as transplantation has become more successful, the number of candidates seeking this treatment has risen even more dramatically. Based on Organ Procurement Transplant Network (OPTN) data as of January 11, 2002, the waiting time for a cadaveric renal transplant has grown to a mean of 422 d for patients with blood type AB and 1453 d for patients with blood type O. As of May 1, 2002, there were 51,978 individuals awaiting renal transplants in the United States. In 2001, there were 6081 cadaveric donors; more than 15% of those procured grafts were discarded (1), resulting in only 8201 renal transplants and 885 kidney-pancreas transplants; during that same year, there were 6514 living renal transplants performed in the United States.

To deal with the widening gap between supply and demand of cadaveric organs for renal transplantation, efforts to expand the organ donor pool have received increased attention. In this regard, alternative approaches to traditional organ donor selection have been proposed (Table1). These measures may be beneficial in terms of increasing the number of donors and decreasing the waiting time. However, deviation from the standard method of cadaver donor selection is not without possible negative impact on graft survival. Despite the fact that these nontraditional or expanded criteria donors (ECD) are more expensive to obtain and use than ideal cadaveric renal transplantation, it is a less expensive alternative for renal replacement therapy than dialysis in the long run, even when the improved quality of life after transplantation is not considered (2). Thus, we will review the potential impact of the expansion of the organ donor pool on renal graft function and survival. In addition, we will also review the impact of newer approaches to living donor kidney transplantation.

Donor Age. Graft outcome in terms of chronic allograft dysfunction is one of the ultimate endpoints that affect donor selection criteria and therapeutic strategies in the recipient. Despite the dramatic improvement in the short-term renal allograft survival since the introduction of calcineurin inhibitors and other novel immunosuppressants such as target of rapamycin (TOR) inhibitors, long-term allograft survival rates have improved only slightly. Chronic allograft nephropathy, the most common cause of long-term allograft dysfunction, may be secondary to antigen-dependent and/or antigen-independent mechanisms (3–9). Antigen-independent donor-related risk factors for poor graft outcome are multiple, including old age, female gender, and black race. Such factors may have an impact on glomerular size, and glomerular hypertrophy/hyperfiltration has been proposed as an underlying mechanism for chronic renal allograft dysfunction (10,11). Abdi *et al.* (12) measured baseline glomerular size and tried to correlate it with long-term graft survival. The glomerular size was measured on renal biopsy specimens obtained intraoperatively at approximately 1 h after perfusion using the maximal planar glomerular tuft area as the variable to be assessed. Ninety-six donor-recipient pairs were analyzed. The follow-up at 4 yr showed that one of the alloantigen-independent factors that was correlated with chronic allograft dysfunction was a larger baseline glomerular size. This morphologic risk factor was found to be related to donor age, with younger donors having smaller glomeruli; however, the effect of donor age was not addressed separately in this study. The initial report of the United Network for Organ Sharing (UNOS) Registry between October 1987 and December 1993 showed donor age as having a less striking effect on graft survival of living donors (13). Other studies were in agreement with this conclusion (14,16–17). However, it should be noted that living donors must pass a rigorous screening procedure designed to assure that they will not be harmed; thus these older living donors are likely to be healthier than is generally true for their age. Virtually all studies indicate that older donor age has an adverse effect on graft survival (15,18–23). At the other end of the spectrum, kidneys from very young donors also are associated with poor outcome, likely related to technical complications and graft thrombosis (24). It is clear now that kidneys from old or very young cadaveric donors (ages <10 yr or ≥ 55 yr) have been associated with diminished long-term graft survival (13,18,25,26). Analysis of UNOS data in 2000 showed that the 5-yr graft survival rate of patients receiving cadaveric kidneys from donors over age 60 yr was 50%, compared with the graft

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Table 1. Alternative criteria to traditional donor selection

- Accepting older and non–heart-beating donors
- Donors with longstanding hypertension
- Donors with renal dysfunction, diabetes, or anatomic anomalies
- Use of bilateral renal allografts from donors with impaired renal function
- Exchange of living donor kidneys
- Use of laparoscopic nephrectomy
- Selective use of hepatitis C–positive donors

survival rate of 70% in patients receiving cadaveric kidneys from donors age 19 to 45 yr (Figure 1).

Thus, old and very young cadaveric donor age seems to be associated with a lower long-term graft survival. These factors need to be considered when making decisions regarding expansion of the donor pool. The decrease of graft survival of kidneys for very young or elderly donors is explained in part by reduced functional reserve in these kidneys, making them more vulnerable during procurement, rejection, and calcineurin inhibitor exposure (27).

On the basis of the best serum creatinine and using the Cockcroft-Gault formula, we recommend in elderly donors a creatinine clearance of more than 60 cc/min. In addition, a wedge biopsy containing at least 70 glomeruli should be performed and examined histologically for the degree of glomerular obsolescence, interstitial fibrosis, and arteriolosclerosis; kidneys with significant degrees of glomerular sclerosis, *i.e.*, more than 15%, should not be transplanted as single kidneys (28). In addition, if there is moderate interstitial fibrosis and arteriolar hyalinosis, the kidney should be discarded. Best results are also obtained when cold storage time is limited to less than 24 h. Longer ischemic times can be achieved with pulsatile pump perfusion. We recommend an allograft flow greater than 100 cc/min with a calculated vascular resistance

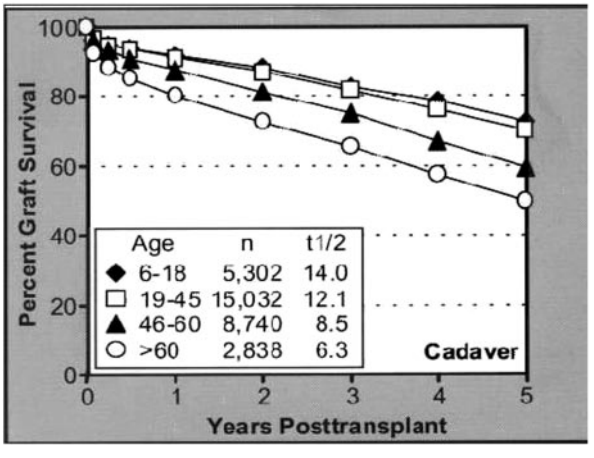

Figure 1. Effect of donor age on first cadaver donor transplant results (1996 to 2000). Reprinted with permission from Cecka JM: The UNOS scientific renal transplant registry. *Clin Transpl* 11: 2001.

less than 0.3 and a systolic perfusion pressure less than 50 mmHg. Finally, kidneys from elderly donors should perhaps be transplanted into age-matched recipients, because these patients require less immunosuppression.

Non–Heart-Beating Donors. Death in heart-beating donors is diagnosed according to brain death criteria. For non–heart-beating donors, also known as Donation After Cardiac Death (DCD), the diagnosis of death is based on cardiac criteria: an irreversible cardiac arrest, an extended period of waiting after cessation of cardiac massage, and artificial ventilation are needed to create a situation that is equivalent to brain death (29,30).

In the early days of transplantation, before the introduction of the concept of brain death, non–heart-beating donors were the main source of kidneys. When the concept of brain death was established, non–heart-beating donors were abandoned and kidneys were procured primarily from heart-beating donors. The proposal to use non–heart-beating donors was reintroduced in 1982 given the shortage of kidneys (29).

As far as short-term graft outcome is concerned, a common finding among several studies was the statistically significant higher prevalence of delayed graft function in the non–heart-beating group when compared with the heart-beating group (16,29,31,32). As for primary graft failure, defined as a graft that never functioned, some studies showed comparable incidence between the two groups (29,31,33). But, Cho *et al.* (34) demonstrated in their multicenter comparative study that primary nonfunction occurred in 4% of recipients of kidneys from donors without heartbeats compared with 1% of the recipients of kidneys from donors with heartbeats ($P < 0.001$). In addition, the serum creatinine of recipients at discharge was significantly higher in the former group. More recipients of kidneys from donors without heartbeats needed dialysis in the first week (48% *versus* 22%; $P < 0.001$). However, when long-term graft survival was analyzed, no statistically significant difference was found between heart-beating and non–heart-beating groups at 2 yr, and graft function at 1 yr assessed by serum creatinine was similar between the two groups. The authors concluded that the disadvantage associated with the use of non–heart-beating donors, *i.e.*, primary graft failure, could be avoided if poor kidneys were preemptively discarded. Most recently Weber *et al.* (35) compared 122 kidney transplant patients involving donors without a heartbeat with a similar group of patients who were matched according to age, gender, number of transplantations, and calendar year period of transplantation and donors with a heartbeat. They again observed a high incidence of delayed graft function (48.4%) in patients who received kidneys from donors without a heartbeat, compared with 23.8% in patients receiving kidneys from donors with a heartbeat. It is interesting, however, that the rate of graft survival at 10 yr was 78.7% of kidneys from donors without a heartbeat, compared with 76.7% for kidneys from donors with a heartbeat. Primary nonfunction occurred in both groups; the incidence was 5.7% of all kidneys from donors without a heartbeat, compared with 4.9% of all those from donors with a heartbeat ($P = 0.99$). In an accompanying editorial, Cecka (36) noted that despite a high percentage of delayed graft function

in that particular study, the graft survival was not affected. Graft survival rates after 15 yr after transplantation were similar in both cohorts of recipients with donors with or without heartbeats.

Several tests have been developed in this regard: the tetrazolium test (37), which measures the metabolic activity of tubules, proton magnetic resonance spectroscopy (38), and measurement of α-glutathione S-transferase activity, which was shown by Kootstra *et al.* (29) to be a reliable parameter to discriminate between functioning and nonfunctioning grafts. The study results also showed that several factors besides the presence or absence of a heartbeat in the donor could adversely affect the graft outcome. These factors included the following: old recipient and donor age; greater than 20% peak panel-reactive antibody; obesity in the recipient; black race in the donor; higher number of HLA mismatches; cold ischemia time >30 h; and cause of death in the donor with a better outcome for kidneys of donors who died of trauma. Since their observation, they reported that the supply of cadaveric kidneys has increased by 40% since they started to recover kidneys from non–heart-beating donors and that measuring α-glutathione S-transferase, an enzyme specific for damage of proximal tubular cells within the kidney, is a promising viability assessment test.

Despite a higher incidence of delayed graft function in the non–heart-beating group, other studies revealed similar results in terms of long-term graft survival between heart-beating and non–heart-beating groups at 1 and 3 yr. Patient survival rates were also comparable between the two groups (32,39,40). The use of extracorporeal bypass and *in situ* organ profusion with double balloon catheter and minimization of the duration of cold ischemia time are the main contributing factors for this clinical success (29,34,37). We recommend donors less than 60 yr and greater than 1 yr of age, who have been extubated and have died in a hospital ICU free of sepsis, who are known to be HIV-negative, and with minimal cold ischemia time. Given the above encouraging results, transplant centers have been encouraged to invest more in the non–heart-beating donors as a source of renal allografts. However, longer follow-up is needed to address the issue of long-term outcomes.

Hypertension and Diabetes. The imbalance between the number of candidates on the cadaver kidney waiting list and the number of cadaver donors has prompted the expansion of the criteria for organ donation to include cadaveric donors with diabetes mellitus or hypertension.

Madden *et al.* (41) retrospectively analyzed cadaveric kidneys transplanted at the University of Cincinnati Medical Center and The Christ Hospital from 1984 through 1991. Eighty-eight patients received cadaveric kidneys from non-ideal donors, defined as age >50 yr, with a history of diabetes mellitus and/or a history of hypertension (group 1). This group was compared with 440 recipients of ideal donor kidneys (group 2). The study results demonstrated that the outcome of renal allografts in terms of 5-yr survival was lower in group 1 but did not reach statistical significance.

When re-transplants were considered alone, differences in survival increased with time, but the number of recipients in group 1 was too small to show statistical significance. However, when risk factors were analyzed separately, allograft survival was significantly decreased in the subgroup of recipients from old donors (age, >50 yr) compared with group 2 ($P = 0.01$). This significance disappeared when re transplants were excluded. The difference, considering other risk factors, was not statistically significant, despite a lower survival rate in the recipients from non-ideal donors. Here too, the number of the patients studied was small. The incidence of acute tubular necrosis (ATN) was comparable between the two groups, but the incidence of rejection in the first 12 mo was significantly higher in group 1 ($P = 0.01$).

Other surrogate endpoints of allograft outcome, such as serum creatinine, creatinine clearance, extent of glomerular sclerosis, interstitial fibrosis on biopsy specimens, and proteinuria were not analyzed. The results of this study, while promising, need a longer followup period, a larger number of patients and further supportive studies before organs from non-ideal donors are routinely recovered.

The recovery of organs from donors with mild hypertension could have great impact, because it is believed that 10% of the adult US population is hypertensive. In a previous study, Mascaretti *et al.* (42) compared 67 recipients of cadaver kidneys from hypertensive donors transplanted between 1983 and 1989 in Italy with 539 patients transplanted in the same period from non-hypertensive donors. They showed a lower, but not statistically significant, difference in patient and graft survival at 2 yr, worse kidney function as assessed by serum creatinine at 1 mo ($P = 0.01$), and higher frequency of early rejection episodes ($P = 0.004$) in donors with hypertension, compared with non-hypertensive donors. The serum creatinine at 6 and 12 mo was comparable between the 2 groups. However, several limitations exist: no data were available on the duration and the treatment of hypertension, information about pretransplant biopsy results were not reported, and more donors in group 1 died of cerebral vascular accident than in group 2 ($P = 0.05$).

It is clear from these studies that recovery of kidneys for transplantation from non-ideal donors remains a major concern for the transplant team. Some centers biopsy the donor kidney to determine its suitability for transplantation. This approach has been advocated by UNOS (43). However, Ratner *et al.* (44) were unable to demonstrate the predictive value of a pretransplant biopsy in terms of graft outcome. They compared 44 recipients of kidneys from hypertensive cadaveric donors with 43 recipients of kidneys from normotensive cadaveric donors. Overall actuarial graft survival was significantly worse in the hypertensive group ($P < 0.001$) at 1 yr; this was largely due to a significant difference in the incidence of primary nonfunction ($P = 0.03$), whereas the incidence of delayed function did not differ between the two groups. Postperfusion biopsies revealed significantly more pathology in the kidneys from hypertensive donors. However, these findings did not correlate with graft survival at 3 yr, primary nonfunction, or delayed function.

With regard to diabetic cadaver kidney donors, previous studies have shown that diabetic nephropathy lesions were reversible after transplantation of a diabetic kidney into a

nondiabetic recipient (45,46). Orlowski *et al.* (47) reported two cases of renal transplantation from diabetic cadaver donors. The first donor was a 48-yr-old type II diabetic woman who was normotensive, diet controlled, and blind secondary to diabetic retinopathy. Her renal biopsy was normal. The kidney was transplanted into a 44-yr-old type I diabetic patient. The graft functioned immediately and for 67 mo before the patient died, with a working kidney, of myocardial infarction. The second donor was a 12-yr-old insulin-dependent diabetic patient who had no diabetic changes on the pretransplant biopsy. After transplantation, the graft functioned immediately and for 44 mo before being lost to chronic rejection.

In a recent report, Fedusca (48) showed that diabetic donor kidneys had a significantly lower 1-yr survival rate compared with that of controls, whereas kidneys from hypertensive donors had slightly poorer graft survival.

Again, we recommend donors with mild hypertension and diabetes mellitus of short duration, a creatinine clearance of more than 60 cc/min, the absence of proteinuria, a wedge biopsy indicating less than 15% glomerulosclerosis, and with mild degrees of interstitial fibrosis and arteriolar hyalinosis. Donor grafts with moderate or severe interstitial fibrosis or arteriolar hyalinosis should be discarded. If the cold ischemia time is greater than 24 h, pulsatile pump perfusion should be used to evaluate the characteristics of the graft.

More recent studies have indicated that selective high-risk donors can be used to overcome the organ shortage and that more effort is needed to develop preoperative tests for the prediction of the postoperative graft outcome (49,50).

Conclusions concerning recovery of kidneys from non-ideal donors should be carefully interpreted; while awaiting better studies, strict and prudent donor evaluation is imperative while good long-term graft outcome remains the ultimate transplantation endpoint.

Finally, Sells (51) suggests that obtaining informed consent from recipients of marginal donor organs is mandatory when donor-related risk factors that may potentially adversely affect graft outcome are known.

Anatomic Anomalies. Reported anatomical abnormalities in cadaver renal transplant donors include hydronephrosis, horseshoe and polycystic kidneys (52,53). The use of kidneys from living donors with multiple arteries has been previously described (54).

The discovery of renal vascular anomalies during evaluation of potential kidney donors is not infrequent. Renal artery aneurysm is encountered in 1% of patients undergoing arteriography (55,56), and other common findings, such as fibromuscular hyperplasia and atherosclerotic arterial lesion, have a 3 to 6% reported incidence (57). The challenge in such cases is to repair the anomalies without adversely affecting the allograft outcome. Early reports emphasized the risk of rupture and the difficulty of doing such repairs (58). However, the experience of transplant surgeons and the developments in microsurgery have yielded better outcomes for these kidney transplantations (53,59).

Beradinelli *et al.* (53) reviewed 368 marginal kidneys, defined as kidneys with multiple arteries, with bifid collecting systems, and horseshoe kidneys, transplanted between 1969 and 1994 at the Policlinico University Hospital in Milan, Italy. Eight kidneys had double ureters, and two separate ureterocystoneostomies with an antireflux technique were performed without any surgical problems. Two indivisible horseshoe kidneys were transplanted *en bloc*. The immediate postoperative period was excellent and free of complications; however, both grafts were lost (at the 25^{th} and 61^{st} posttransplant months) due to rejection. The remaining 358 kidneys with multiple renal arteries were transplanted after *ex vivo* arterioplasty with either a primary revascularization in 267 cases or bench surgery reconstruction in 91 cases. The overall failures related to surgical complications in the series of primary revascularization grafts were 15 (5.6%), most of them occurred in the initial series of vascular repair. The results showed similar 1-yr graft survival rate in recipients of marginal kidneys and recipients of normal kidneys transplanted during the same period (83 to 86%). The above results are encouraging, advocating the beneficial effect of *ex vivo* arterioplasty in circumventing the shortage of kidney donation without affecting graft outcome.

More recently, Nahas *et al.* (59) reviewed their experience of 11 transplant recipients from living donors with renal artery anomalies diagnosed on arteriography. Included were aneurysms, atherosclerotic plaques, fibromuscular dysplasia, and polar artery stenosis. All abnormalities were corrected under hypothermic conditions during bench surgery, except three cases of ostial atherosclerotic plaque, which were left in the donors. All patients had immediate diuresis, and no delayed graft function was observed. One recipient died of transplant-unrelated cause, and three allografts were lost: one to acute vasculopathy, one to renal artery thrombosis, and one to recurrence of the hemolytic-uremic syndrome. The remaining patients were normotensive with a mean serum creatinine of 1.4 mg/dl (mean follow-up, 66 mo). In patients with unilateral fibromuscular dysplasia, the development of the disease in the contralateral renal artery is unusual; only one case has been documented thus far (60).

Other studies showed that microsurgical reconstruction of multiple renal arteries yields excellent results (61,62). The major concern in living renal transplantation remains the protection of the donor. The authors therefore concluded that living donors with extensive vascular disease should not be selected, mainly due to the risk of progression of atherosclerotic disease in a solitary kidney (63).

The Use of Bilateral Renal Allografts from Donors with Impaired Renal Function. Some transplant centers expanded their acceptable criteria to include donors (either adult or pediatric) with suboptimal renal mass by transplanting both kidneys in the same recipient, allowing for the salvage of suboptimal kidneys that would otherwise be discarded (64–66).

Double transplants, *i.e.*, transplanting both kidneys from the same donor into one recipient, is a well-known procedure that has been performed numerous times and in multiple centers (66). However, the majority of these transplants consist of pediatric *en bloc* kidneys. Recently, the number of adult-to-adult dual transplants has markedly increased (64). When to

use ECD kidneys for dual *versus* single kidney transplants is currently unclear.

Alfrey *et al.* (64) tried to answer this question by retrospectively reviewing all adult cadaveric renal transplantations performed at Stanford University Medical Center between January 1995 and November 1996. Of 126 adult CRT, 52 patients received ECD "kidneys that nobody wanted." Fifteen of these were recipients of dual kidney transplants and 37 were recipients of single transplants.

Analysis of donor and recipient related factors showed that a donor creatinine clearance on admission below 90 ml/mn, a donor age $\geq$59 yr, and a cold ischemia time $>$24 h were independent risk factors for delayed graft function when ECD kidneys were transplanted as single rather than dual kidneys. However, graft survival and mean serum creatinine at 1 yr were similar between the two groups. When compared with recipients from cadaveric ideal donors transplanted during the same period, patients with dual transplants had a significantly higher mean serum creatinine at 1 yr but similar mean serum creatinine at 18 mo and graft survival rates at 1 yr. The major improvement in using the ECD kidneys as dual *versus* single grafts was a decrease in the incidence of delayed graft function.

Most studies describe improvement in short-term (1 yr) and long-term outcome in patients without delayed graft function *versus* patients with delayed graft function (67–70). Some reports do not document a decrease of graft survival in patients with delayed graft function except in association with acute rejection (71,72). However, if we consider that delayed graft function has a negative impact on long-term renal allograft outcome, old cadaveric donors with poor renal function and prolonged cold ischemia time seem not to be adequate for single transplantation. To accept them as donors for dual transplantation or to discard them is a decision left to the transplant team. The above authors postulate cautious use and the restriction of these dual kidney transplant techniques to patients with limited access to dialysis or those who are functioning poorly on dialysis (64).

It is our recommendation that dual cadaveric kidney transplantation should be used in patients with creatinine clearance of between 40 and 60 ml/min. A wedge biopsy of the graft should show the presence of no more than 15 to 30% of glomerulosclerosis and only mild interstitial fibrosis and arteriolar hyalinosis. If moderate or severe interstitial fibrosis or arteriolar hyalinosis is present, the kidney should be discarded. In grafts with a prolonged cold ischemia time, the kidneys should be put on a pulsatile pump for at least 4 h to evaluate the perfusion characteristics.

Nghien *et al.* (73) reviewed their own 10-yr experience of 78 recipients of *en bloc* transplantation of infant kidneys and found a graft survival rate of 79% with an average serum creatinine of 0.8 mg% and 24-h proteinuria of 156 mg%. Five *en bloc* kidneys were lost due to thrombosis (6.4%), and renal artery stenosis was described in seven patients. In addition, hyperfiltration was not observed, possibly related to the rapid growth of the pediatric kidney.

Hobart *et al.* (74) also reviewed 33 pediatric *en bloc* kidneys transplanted into adult recipients. In *en bloc* pediatric grafts compared with single adult cadaveric donors, survival rates were 87.3 *versus* 88.6% at 1 yr, 87.3% *versus* 84.2% at 3 yr, and 54.3 *versus* 72.2% at 5 yr. Again, they warn about the increased risk of early and late vascular complications. However, young infant recipients have particularly poor graft survival rates when they receive grafts from age-matched cadaver donors (23,24).

In view of the above results, we recommend that *en bloc* infant kidneys be used for transplantation in adult recipients.

Living Unrelated Donors and Exchange of Living Donor Kidneys. Altruistic emotionally related donation is currently accepted by most of the North American renal transplant centers, mainly after favorable results of living unrelated kidney donation have been reported (75–82) and recently confirmed by a review of data from the UNOS Renal Transplant Registry (83).

Most series showed that wives were more likely to be donors than husbands (84,85). As of November 2001, there were 2355 wife-to-husband and 1095 husband-to-wife renal transplants reported since 1987 in the United States. The actuarial graft survival was the same at 1 yr (92.8% *versus* 92.5%) and at 5 yr (76.4% *versus* 75.6%); at 10 yr, however, there was statistically significant difference (57.4% *versus* 48%), most likely due to the small number of husband donors (86).

ABO blood group compatibility is required for most successful renal transplantation (87); therefore, several altruistic emotionally related donations may be impossible because of incompatible blood groups. In this regard, kidney exchanges between pairs of spouses were recently proposed to achieve ABO compatibility and to expand the living donor pool (88). In some centers, other suggestions include a family member donating a kidney to the cadaveric pool and then the spouse coming to the top of the list for the next appropriate ABO compatible kidney. A pilot program to permit this type of exchange was initiated in UNOS region 1 in 2001 (89).

An exchange-donor program has been used since 1991 in Korea (90). Sixty-one patients have been transplanted from exchange donors between 1991 and 1997 at Hanyang University Hospital Transplantation Unit. At a mean follow-up of 30.8 mo, 59 patients out of 61 were still alive and two died of accelerated acute rejection and sepsis after transplantation. The mean serum creatinine was 1.64 mg/dl, and the graft survival rates at 1 and 5 yr were 92.12% and 80.27%, respectively. A control group formed of 161 recipients from living-related donors and transplanted during the same period showed similar results. The authors therefore encourage other transplant centers to adopt an exchange-donor program to avoid extended waiting periods for transplantation and recommend a strict donor selection in which many factors should be considered.

Criteria to accept an exchange donor include:

- Complete lack of any HLA and/or ABO-matched living-related donor
- Prolonged waiting period for a suitable cadaveric donor
- Complete informed consent of the donor and recipient and their family without compulsion
- Age of the exchange donor over 20 yr

- No evidence of a commercial transaction
- Thorough investigation of the identification for renal transplantation in the recipient

Park *et al.* (90), in their recent collaborative study from 3 centers in Korea, showed good results with exchange donor kidney transplantations. From 1991 to 1997, 86 renal transplantations using simple donor exchange and 24 using living donor pool exchange were performed. The causes of donor exchange were ABO blood type incompatibility in 75.5%, poor HLA match in case of spousal donation in 13.6%, and positive lymphocyte crossmatch in 10.9%. Graft outcome in all cases was comparable to that of recipients from other living donors (related and unrelated without exchange).

However, there is a major ethical concern about blood group O transplant candidates. It is likely that the patient seeking a swap from the cadaver list will be blood type O and that the potential living donor will be blood group A, B, or AB, because those who are blood type O are the universal donors. Thus, the recipient who will receive the living donor graft will be non-O and the recipient of the cadaver graft will be O. The blood type O cadaver list candidates already have the longest waiting times; therefore, they have a legitimate complaint that these types of swaps will be detrimental to them.

Laparoscopic Nephrectomy. Laparoscopic nephrectomy was proposed as an alternative to the standard open approach to minimize short-term risk to the kidney donor decreasing the hospital stay, convalescence period with time away from the job, and perioperative pain because of the small incision.

Philosophe *et al.* (91) at the University of Maryland reviewed 193 recipients of donor laparoscopic nephrectomy and compared them with 168 recipients of kidneys procured by the open technique. They found no difference in graft or patient survival at 2 yr. In addition, the incidence of delayed graft function and mean serum creatinine were similar in both groups. The rate of ureteral complications in the recipients that required operative repair was significantly higher in the laparoscopic group, compared with the open donor nephrectomy group (7.7% *versus* 0.6%). There was, however, a learning curve with time, with only one ureteral complication in the last 63 patients.

Montgomery *et al.* (92) compared the results between the first 100 and the last 100 laparoscopic donor nephrectomies performed at Johns Hopkins Hospital between January 1995 and July 1999. There was no difference in patient survival between the two groups. A total of six grafts were lost in the first 100 kidneys procured by the laparoscopic technique, compared with two graft losses in the last 100 patients. Again, a learning curve was seen with time as far as ureteral complications, with seven occurrences in the first 100 cases compared with three in the last 100 cases.

Despite the above favorable report, there is concern about the potential effect of increased intraabdominal pressure from the induced pneumoperitoneum on lowering the renal blood flow and consequently causing renal failure (93–95). In addition, the excessive manipulation and extraction of the kidney during laparoscopic surgery may be correlated with expanded chronic allograft nephropathy (96,97). A recent survey of US transplant centers revealed that there are few complications from all types of donor nephrectomies but the laparoscopic technique tends to have higher complication rates (98).

Hepatitis-C. Hepatitis C is the most important cause of chronic liver disease in the United States, with an estimated number of four million people currently infected (99). In addition, 10 to 20% of hemodialysis patients are chronically infected with hepatitis C (100). Liver failure in transplant recipients in the majority of cases is secondary to hepatitis C and is a major cause of death in patients in the late posttransplant period. Approximately 4 to 8% of organ donors, depending on the geographic region, test positive for the second generation ELISA test against HCV (EIA-2 test) (101). In urban areas, up to 15% have been found to be positive among organ donors. Some donors with positive HCV EIA-2 (screening test) do not have evidence of true infection when further screened by PCR and by RIBA assays. Thus, in centers where only the EIA-2 is used, donors may be unnecessarily wasted.

Longitudinal studies of HCV-positive renal transplant recipients have demonstrated different clinical outcomes, in part dependent on the duration of the study.

Kliem *et al.* (102) showed no increase in mortality or morbidity in transplant recipients with preexisting hepatitis C infection, compared with a control group of recipients who were HCV-negative.

Hanafusa *et al.* (103) found a higher incidence of liver dysfunction in transplant recipients with chronic hepatitis C when compared with HCV-negative recipients (92% *versus* 55%). The mortality rate was also higher in the recipients with hepatitis C compared with the noninfected group. Although this was not apparent in the first decade (80.7% *versus* 88.9%; $P = 0.44$), it was statistically significant in the second decade (53.9% *versus* 87.6%; $P < 0.05$). However, the critically important comparison of survival differences between HCV-positive patients on dialysis *versus* HCV-positive transplant recipients has not been robustly examined. For this reason, HCV-positive renal transplant candidates should be informed that increased morbidity and mortality at later stages posttransplant are a possible outcome.

If candidates with HCV infection are to receive renal allografts, is it reasonable to utilize HCV-positive donors, thus expanding the donor pool? It is well known that the transmission of hepatitis C occurs with high efficiency when a kidney from a hepatitis C–positive donor is given to a hepatitis C–negative recipient (104). Morales *et al.* (105) found no statistical difference in posttransplant liver disease, graft survival, or patient survival among 64 recipients who were hepatitis C–positive and received hepatitis C–positive kidneys when compared with hepatitis C–positive recipients who received hepatitis C–negative kidneys. It is notable, however, that the number of patients was small and the duration of the study too short. In a larger study of 110 patients who were hepatitis C–positive, 61 of whom received hepatitis C–positive and 49 hepatitis C–negative organs, Oldach *et al.* (106) also found no difference in patient survival or allograft survival at 5 yr, even though four patients developed supra infections in the D^+ to

R^+ group. In that particular study, estimated donor-virus supra infection rate was 15 to 25%, substantially lower than that occurring where HCV-negative naïve recipients are transplanted with an HCV-positive donor.

In light of these findings, recipients and their families should be aware of the potential risks and benefits of receiving an infected organ at the time of the informed consent.

Conclusion

The shortage of kidney donors exponentially increases every year. To circumvent this shortage of kidneys, we have reviewed several proposed alternatives to expand the donor pool. These alternatives include very young and older donors, the use of dual transplant from donors with impaired renal function, patients with renal anatomic anomalies, the exchange of living donor kidneys, the use of non–heart-beating donors, and using donors who are HCV-positive.

In addition, the UNOS board has recently approved preferential allocation of kidneys procured from ECD primarily to pre-informed patients with zero-antigen mismatch. Secondarily, the allocation should go to patients with limited life expectancy due to graft failure and, finally, to patients who have been on the waiting list for an extended period of time (1). Each of these alternatives includes specific risks to the graft and to the recipient that must be considered individually. Successful kidney transplantation greatly improves the quality of life in almost all patients with end-stage renal disease. This benefit must be carefully weighed against the risks of using marginal or expanded donors.

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