Transpl Int (1998) 11: 164–168

INVITED REVIEW

D. C. Dafoe
E. J. Alfrey

Dual renal grafts: expansion of the donor pool from an overlooked source

Received: 23 September 1997
Accepted: 10 October 1997

D. C. Dafoe[1] (✉) · E. J. Alfrey
Division of Transplantation,
Department of Surgery,
Stanford University School of Medicine,
300 Pasteur Drive, Room H2104,
Stanford, CA 94305-5342, USA

Corresponding address:
[1] Stanford Multi-Organ Transplant Center,
750 Welch Road, Suite 200,
Palo Alto, CA 94304, USA

Abstract This is a review of the emerging practice of dual renal allografting. In the setting of the expanded criteria cadaveric (and usually older) donor with inadequate function to allow single kidney transplantation, both kidneys have been transplanted into a single recipient. The recipient and donor have often been matched for age and size as dictated by the concept of nephron dosing. The reported results of dual grafting are excellent and statistically comparable to contemporaneous single cadaveric grafts. Criteria are evolving regarding when to apply single or dual grafting. Wider acceptance of dual renal grafting could have a significant impact on the cadaver kidney shortage.

Key words Dual renal grafts, transplantation · Transplantation, dual renal grafts · Elderly kidney donor, dual graft

The worsening donor shortage

Renal transplantation is considered the treatment of choice for patients with end-stage renal disease (ESRD) [25]. A successful renal transplant will improve the recipient's quality of life and provide economic benefits to society as compared to other ESRD treatment modalities [16]. According to the1996 Annual Report of the United Network for Organ Sharing (UNOS), the actual 1-year patient and graft survival rates for recipients of cadaveric grafts undergoing transplantation in 1994 were 94 % and 84 %, respectively [1]. These excellent results and the decreased morbidity associated with renal transplantation, particularly with newer immunosuppressive agents [19], has increased the demand for renal grafts. UNOS reports that 11,810 renal transplantations were performed in the United Sates in 1995. Cadaveric donation was the source of these kidney grafts 73 % of the time. The remaining grafts were from living related donors (LRD; 89 %) and living unrelated donors (LURD, also known as emotionally related donors; 11 %). The latter group has tripled since1988. Despite the use of LURDs, other expanded criteria donors (ECDs), and legislative initiatives (e.g., required request), the cadaveric donor supply has risen only very gradually, by about 4 % a year from 1988 to 1995. During this same time period, the waiting list burgeoned 170 %. At last tally, there were over 34,000 candidates on the cadaver kidney waiting list in the United States. The median waiting time is approximately 2.3 years. European countries have also experienced a dire shortfall of cadaveric grafts [7].

In addition to the shortage of cadaveric grafts, the donor pool has changed qualitatively. Most notably, the average donor is older. Nationally, in the United States, the percentage of donors above 50 years of age increased from 15 % in 1990 to about 25 % in 1995 [1]. The mean age of cadaveric donors in the California Transplant Donor Network, an organ procurement organization (OPO) serving a population of 11 million in Northern California, was 26 years in 1990 and 39 years in 1994 [5]. With the decrease in accidental deaths that has come about as a consequence of mandatory sealt belt laws, air bags and tougher measures against drunk driving, cerebrovascular accidents (CVA) have become the predominant cause of death among cadaveric donors. CVAs occur in an older cohort of donors with hypertension and systemic vascular disease. There is an understandable reluctance on the part of transplant surgeons and physicians to use renal grafts from these donors. This reluctance is supported by the transplantation literature. Reported success rates for renal transplants from donors below 12 or above 65 years of age are significantly reduced as compared to grafts from intermediately aged donors [9]. According to 1992 UNOS data, the national discard rate for cadaver kidneys from donors above 55 years of age was 23 %. In 1994, an OPO in the state of Maryland discarded 45 % of grafts from donors above 60 years of age [14]. An Australian study found that 46 % of patients (92/198) rendered braindead from a CVA met eligibility criteria for renal donation, but in only one instance were kidneys procured and transplanted [24]. Most of these patients were over 60 years of age.

In light of the widening gap between the growing number of transplant candidates and the insuffcent supply of cadaver kidneys, progressive transplant centers have reconsidered the use of grafts that were once dismissed a priori [12, 17, 23]. Such grafts are procured from donors with hypertension, diabetes of short duration, elevated serum creatinine (SCr), a history of treatment with pressors for hemodynamic instability, disseminated intravascular coagulation, and worrisome viral serologies (e.g., hepatitis B core antibody-positive). These grafts may have reconstructable anatomic abnormalities, prolonged cold storage time, and/or biopsy findings of concern (e.g., glomerulosclerosis). Nonheartbeating donors have provided many suitable grafts, but donor criteria and associated logistical issues remain controversial [21]. To address the cadaveric graft deficit, transplant surgeons at Johns Hopkins in Baltimore have even boldly proposed to surgically divide a single renal graft and transplant each half into two recipients [27].

Use of ECDs

In 1995–1996, we adopted an aggressive stance in the acceptance of cadaveric grafts and became the court of last appeal for our regional OPO. We proceeded to transplant grafts that we referred to as "kidneys that nobody wanted" (KNW). The KNWs were operationally defined as cadaveric donor grafts that were declined by the three other transplant centers served by our OPO. Each of these centers is well regarded and active, carrying out about 30–220 renal transplants annually. In 15 months we accumulated an experience with 31 single renal transplants from ECDs [17]. The results we obtained using ECDs were compared to 56 conventional kidney transplantations performed contemporaneously at our center (control group). Significant differences were found between the KNWs and the control group in mean donor age (52 ± 7 vs 40 ± 17 years); lowest total 4-h urine output in the donor (327 ± 208 vs 507 ± 437 ml), and SCr 1 month after transplantation (2.6 ± 1.8 vs 1.8 ± 1 mg/dl). No differences existed between the groups in the incidence of delayed graft function (DGF, defined as the need for one or more dialysis treatments after transplantation) or recipient SCr at 6 and 12 months. Furthermore, 1-year patient (100 % vs 95 %) and graft (97 % vs 91 %) survival rates were also comparable.

We were emboldened by these good results. As we evolved into a repository for ECDs, opportunities for dual grafting presented themselves. (We would be remiss not to acknowledge that the idea of dual grafting was first proposed by Dr. Stephen Bartlett, a transplant surgeon at the University of Maryland.) Typically, both ECD renal grafts were offered to our transplant center by the OPO. The offer was exclusive since other transplant centers had "passed", due to the appropriate concern that a single ECD graft would provide inadequate function. With both kidneys available to us, we could minimize cold storage time and exercise discretion in our selection of a candidate for dual grafting. All candidates gave informed consent. The early dual grafting experience yielded excellent outcomes, so we have continued the practice. As our series has grown (currently at 24 dual-grafted recipients), we have refined our surgical techniques, developed recipient criteria, and initiated a formal study of dual graft physiology.

Conceptual considerations in the use of dual renal grafts

Humans are born with an average of 620,000 nephrons (range 330,000–1,100,000) [20]. Not all kidneys are created equal. There are individual differences in nephron number related to kidney weight, body weight, and surface area. Nephrons do not proliferate, but it is well known that a single kidney has the capacity for impressive compensatory hypertrophy. For example, immediately after uninephrectomy in a LRD, the glomerular filtration rate (GFR) drops by half (e.g., from 120 to 60 ml/min). Rapid hemodynamic changes increase GFR within minutes, but a new plateau of higher GFR is established within several weeks (e.g., 80 ml/min). Dual grafting has a long-standing precedent in the transplantation of pediatric kidneys en bloc with a common aorta and vena cava. Since the 1970s, pediatric donors ranging in age from 12 months to 5 years have provided both kidneys for transplantation into a single recipient. Advocates of this technically demanding approach have reported satisfactory outcomes despite the higher risks of surgical complications such as thrombosis and ureteral leak [4, 22]. It has been said that pediatric grafts are resilient, with the potential for lifetime function. In contrast, at the other end of the age spectrum, older

ECD renal grafts are senescent, lacking the regenerative properties of pediatric grafts. This fact makes adult donor dual grafting controversial.

In the context of dual grafting, it is important to mention the nephron dose concept. This concept maintains that a reduction in renal mass results in hyperfiltration and hemodynamically mediated glomerular injury [3]. Chronic hyperfiltration produces hypertension, proteinuria, and progressive loss of function. The associated histological changes, intimal thickening, glomerulosclerosis, and tubular atrophy are indistinguishable from chronic rejection [11]. In renal transplantation, renal mass is further reduced by preservation and reperfusion injury, ongoing hypertension, cyclosporin/tacrolimus toxicity, and rejection. As the number of nephrons diminishes, the cycle, and functional loss, is perpetuated. The hyperfiltration concept in transplantation is supported by data showing that graft survival suffers when the renal mass is reduced, for example, when the kidney-to-recipient weight ratio is below 2.0 g/kg [26]. The intuitive value of a sufficient nephron dose is underscored by research showing that dual renal grafting in rats avoids the clinical syndrome of deteriorating renal function seen in recipients of a single graft [18]. The need for an adequate renal mass in transplantation does not per se justify dual grafting but, rather, emphasizes the folly of ECD single grafting.

In our experience, the opportunity for dual grafting has often arisen when the donor is over 60 years of age. With regard to renal reserve, it is widely appreciated that chronological age may not correlate with physiological age in specific individuals. For instance, hypertension, cigarette smoking, and low cardiac output may severely depress renal function in a 58-year-old donor whereas a vigorous septuagenarian donor with a pristine medical history may have better renal function. Also, since SCr level depends on muscle mass, a low SCr in a female donor of diminutive stature may over-represent renal function. Despite individual donor considerations, advancing age predictably corresponds to a steady decrement in renal function. A rule of thumb is that GFR falls 0.8 ml/min per year. Using the Cockcroft-Gault formula, creatinine clearance (CrCl) – a surrogate for GFR – may be approximated [6]. In this formula, age is a prominent negative factor in the numerator of the equation. However, it must be appreciated that commensurate with the "greying" of cadaveric donors, the average age of ESRD patients has increased too [8]. In 1986, the mean age of patients on dialysis in the United States was 56 years; by 1995, the mean age had risen to 60 years. The idea of age parity between older donors and recipients has intrinsic logic: older donor grafts that might otherwise be discarded may be transplanted into older recipients who might otherwise be denied a kidney transplant.

The bias of one or none

Transplant surgeons and physicians might overcome the entrenched bias against dual grafting with the idea that dual renal grafts represent two halves of a single kidney. Rather than transplant centers declining ECD or older donors altogether, consideration should be given to dual renal grafting. The pros and cons can and should be debated. One may argue that "two suboptimal kidneys are no better than one" or that "a transplant candidate who has waited patiently on the list deserves the best chance of success". Other negative aspects of dual grafting include more time under anesthesia, a larger dissection, and a technical complication rate that is, in theory, twice that of conventional single renal grafting. It can be argued that an age-matching policy places dual grafts from ECDs or older donors into older recipients who are least able to tolerate longer surgery or a higher rate of complications. Since the antigen load is greater, rejection episodes may be more vigorous or frequent. Economic disincentives of dual grafting include a prolonged operating room time and a longer stay in the hospital from more extensive surgery.

The main advantage of dual renal grafting to the community is expansion of the donor pool. Based on our experience, we estimate that the annual number of renal transplants could increase by more than 10 % if dual renal grafting were widely applied. Another major advantage of dual grafting is the shorter waiting time for the recipient. We have practiced age-matching and size-matching between the donor and recipient. This policy is an effort to match nephron dose and metabolic demand. A shorter time on the waiting list may be a worthwhile choice for patients who face a limited lifespan. The inherent obsolescence of older grafts may not come into play in older recipients. Less delicately expressed, the grafts may outlive the recipient. An older individual with ESRD may prefer to spend his or her retirement years off dialysis as the recipient of a successful dual renal transplant that provides more energy for activities, fewer and fluid dietary restrictions, and better ease of travel. As to the cost of dual grafting, we have found a reduced incidence of DGF in our dual renal graft recipients (probably due to limited cold storage and increased nephron number). A lower DGF rate may offset the aforementioned adverse economic consequences of dual grafting. An economic analysis of early dual grafting versus continued dialysis or additional waiting and single grafting is needed.

Technical aspects

Initially, we transplanted both grafts on one side in the extraperitoneal iliac fossa through a standard, but larger, transplant incision. Kinking of vessels was a concern due to the confined space. (In fact, early in our experience, one graft of a dual graft was lost due to venous thrombosis). We then switched to a midline incision carried through the linea alba but leaving the peritoneum unviolated. The preperitoneal space was dissected, exposing the bilateral iliac fossae in a manner described by our group for kidney-pancreas transplantation [15]. With the aid of a self-retaining retractor, the iliac vessels could be readily accessed. The transplants then proceeded in the customary fashion.

Our current technique is a midline incision, transperitoneal approach, and placement of one graft in each of the iliac fossae. Speed is the main reason for the change in technique. The external iliac vessels are used for the vascular anastomoses and the ureters are implanted separately into the bladder employing an extra-vesical technique. To allow percutaneous biopsy with a reduced risk of hemorrhage, a "curtain" of peritoneum is dissected off the lateral abdominal wall and pulled down over the renal graft. Because of postoperative adynamic ileus from retraction of intestines, a nasogastric tube is left in the stomach until peristalsis returns. (This practice differs from conventional single grafts, where a nasogastric tube is not used.) After dual grafting, the urinary catheter is removed in the standard time frame of 48 h after surgery.

Results

The first presentation of dual grafting with adult kidneys in the United States was at a regional surgical meeting in March 1996, with a subsequent publication in October 1996 in a national surgical journal [14]. The short-term results (mean follow-up of 6.6 months) in nine dual graft recipients were discussed. This preliminary report constituted the combined experience of the University of Maryland and ours at Stanford. We found that dual renal grafts provided a mean SCr of 1.6 ± 0.3 mg/dl, a CrCl of 43 ± 3 ml/min per 1.73 m^2, and 100 % graft survival. Since the first reports in 1996 [13, 14], there has been a gradual acceptance and implementation of dual grafting in the United States. UNOS data from 1995 showed that 17 % of all cadaveric kidney transplants (32/8, 598) were non-pediatric dual grafts. This percentage increased to 33 % (76/8, 561) in 1996 [1].

In 1997, at the American Society of Transplant Physicians annual meeting, we at Stanford reported the outcomes in 15 dual graft recipients and compared them to 74 conventional single cadaveric graft recipients (control group) and 37 single ECD renal graft recipients [2]. All transplantations were carried out over the same time period under the same immunosuppressive protocol. Compared to single ECD graft recipients, dual graft recipients had significantly less DGF and graft function was better at 1, 4, and 12 weeks after transplantation. The 1-year patient and graft survival rates were not statistically different between the groups: 94 % and 91 % for controls, 96 % and 81 % for single ECD, and 93 % and 87 % for dual. We identified a subset of ECD single graft recipients that did poorly. The donors to these recipients had a calculated CrCl below 90 ml/min, a donor age above 59 years, and a cold storage time above 24 h. Overall, both dual grafts and conventional single grafts provided comparable excellent results.

Given a specific ECD, when is it advisable to transplant dual grafts into one recipient rather than single grafts into two recipients? Tested criteria do not yet exist. Our current practice is to determine the admission SCr clearance on the donor using the Cockcroft-Gault equation. If the CrCl is above 40 and below 90 ml/min, dual grafting is carried out. This rationale is based on the halving of CrCl by therapeutic levels of cyclosporin or tacrolimus. We have reasoned that a CrCl below 40 ml/min in the prospective cadaveric donor would not provide an adequate nephron dose, even with dual grafting, and a CrCl above 90 would allow single grafting with satisfactory function in the recipient. These criteria must be revisited and will be further refined with time.

Closing thoughts

In summary, dual grafting can provide dialysis independence and graft survival that is comparable to conventional single renal grafts. Dual renal grafts must be tailored to the recipient. Informed consent is essential. We have usually performed dual grafting in older recipients of diminutive stature. However, dual grafting may evolve to include transplantation of ECDs from younger donors into younger recipients. The freedom to select an appropriate recipient is often precluded by the mandated distribution policies of UNOS in the United States [10]. These are equitable policies that have been developed through consensus by the transplant community. Nevertheless, in the setting of ECD grafts or dual grafting, flexibility in recipient selection is necessary. Candidate selection is founded on an analysis of graft nephron dose and recipient characteristics tempered by clinical judgment. An undesirable consequence of generalized dual grafting would be inappropriate dual grafting when a single graft would suffice, thereby further reducing the donor kidney supply. Another adverse consequence, in our opinion, would be a policy of national sharing of dual grafts. Though such a policy may be well intentioned, the additional cold storage time would likely translate into inferior results.

It is imperative for transplant centers that perform dual grafting to study this novel approach in a thoughtful way. To this end, a meeting on dual renal grafting, organized by Dr. Edgar Milford, was held in Boston in the summer of 1997. There was a strong consensus for multi-institutional cooperation in the establishment of a registry of the dual grafting experience. (Co-author, Dr. Edward Alfrey, will be the individual responsible for the maintenance of the registry.) It is likely that dual grafting will find its niche as an acceptable alternative for a subset of ESRD patients who will benefit substantially. In the debate over dual grafting, the concept of matching graft nephron dose and recipient metabolic demand will be a consideration in the optimal allocation of scarce cadaveric grafts.

References

1. 1996 Annual Report of the U.S. Scientific Registry for Transplant Recipients and the Organ Procurement and Transplantation Network-Transplant data; 1988- 1995. UNOS, Richmond, VA, and the Division of Transplantation, Bureau of Health Resources Development, Health Resources and Services Administration, U.S. Department of Health and Human Services, Rockville, MD
2. Alfrey EJ, Lee CM, Scandling JD, Pavlakis MP, Markezich AJ, Dafoe DC (in press) When should expanded criteria donor kidneys be used for single versus dual kidney transplants? Transplantation
3. Brenner BM (1983) Hemodynamically mediated glomerular injury and the progressive nature of glomerular disease. Kidney Int 23: 647–655
4. Bretan PN, Friese C, Goldstein RB, Osorio RW, Tomlanovich S, Amend W, Mathur V, Vincenti F (1997) Immunologic and patient selection strategies for successful utilization of less than 5 kg pediatric donor kidneys – long term experiences with 40 transplants. Transplantation 63: 233–237
5. California Transplant Donor Network 1996 data, Phyllis Weber, executive director
6. Cockcroft DW, Gault MH (1976) Prediction of creatinine clearance from serum creatinine. Nephron16: 31–41
7. Cohen B, DÁmaro J, DeMeester J, Persijn GG (1997) Changing patterns in organ donation in Eurotransplant. Transplant Int 10: 1–6
8. Excerpts from United States Renal Data System (1997) Annual Data Report. The National Institutes of Health, Division of Kidney, Urologic and Hematologic Diseases (Bethesda, MD, April 1997)., II. Incidence and prevalence of ESRD. Am J Kidney Dis 30 [Suppl 1]:S40-S53
9. Gjertson DW (1997) A multi-factor analysis of kidney graft outcomes at one and five years posttransplantation: 1996 UNOS update. In: Cecka JM, Terasaki PI (eds) Clinical transplants 1996. UCLA Tissue Typing Laboratory, Los Angeles, pp 343–360
10. Hauptman PJ, O'Connor KJ (1997) Procurement and allocation of solid organs for transplantation. N Engl J Med 336: 422–431
11. Heemann UW, Azuma H, Tulius SG, MacKenzie H, Brenner BM, Tilney NL (1994) The contribution of reduced functioning mass to chronic kidney allograft dysfunction in rats. Transplantation 58: 1317–1322
12. Jacobi LM, McBride VA, Etheredge EE, McDonald JC, Cooper ES, Frey D, Boudreaux JP, Gonzalez F, VanMeter C, McMillan R, Tesi RJ (1995) The risks, benefits, and costs of expanding donor criteria. Transplantation 60: 1491–1496
13. Johnson LB, Kuo PC, Dafoe DC, Drachenberg CB, Schweitzer EJ, Alfrey EJ, Ridge LA, Salvatierra P, Papadimitriou JC, Mergner WJ, Bartlett ST (1996) The use of bilateral adult renal allografts: a method to optimize function from donor kidneys with suboptimal nephron mass. Transplantation 61: 1261–1263
14. Johnson LB, Kuo PC, Dafoe DC, Schweitzer EJ, Alfrey EJ, Klassen DK, Hoehn-Saric EW, Weir MR, Bartlett ST (1996) Double adult renal allografts: a technique for expansion of the cadaveric donor pool Surgery 120: 580–584
15. Kuo PC, K.N, Alfrey EJ, Scandling JD, Dafoe DC (1995) The utility of retroperitoneal kidney placement in simultaneous kidney pancreas transplantation. Clin Transplant 9: 457–462
16. Laupacis A, Keown P, Pus N, Krueger H, Ferguson B, Wong C, Muirhead N (1996) A study of the quality of life and cost-utility of renal transplantation. Kidney Int 50: 235–242
17. Lee CM, Scandling JD, Shen GK, Salvatierra O, Dafoe DC, Alfrey EJ (1996) The kidneys that nobody wanted. Transplantation 62: 1831–1841
18. MacKenzie HS, Tullius SG, Heemann UW, Azauma H, Rennke HG, Brenner BM, Tilney, NL (1994) Nephron supply is a major determinant of long- term renal allograft outcome in rats. J Clin Invest 94: 2148–2152
19. Morris RE (1996) Beware: shifting paradigms ahead. Lancet 348 [Suppl 2]: 26
20. Nyengaard JR, Bendtsen TF (1992) Glomerular number and size in relation to age, kidney weight, and body surface in normal man. Anat Rec 232: 194–201
21. Orloff MS, Reed AI, Ertruk E, Kruk RA, Paprocki SA, Cimbalo SC, Cerilli J (1994) Nonheartbeating cadaveric organ donation. Ann Surg 220: 578–585
22. Portoles J, Maranes A, Prats D, Torrente J, Marron B, Perez-Contin MJ, Herrero JA, Coronel F, Grimalt J, Barrientos A (1996) Double renal transplant from infant donors. Transplantation 61: 37–40
23. Ratner LE, Kraus E, Magnuson T, Bender JS (1996) Transplantation of kidneys from expanded criteria donors. Surgery 119: 372–377
24. Smith KG, Martyn BN, Walker RG, Davis SM, Francis DM, Becker GJ (1993) The potential for elderly donors to increase renal transplantation rates in Australia. Med J Aust 58: 588–590
25. Suthanthiran M, Strom TB (1994) Renal transplantation. N Engl J Med 331: 365- 376
26. Terasaki PI, Koyama H, Cecka M, Gjertson DW (1994) The hyperfiltration hypothesis in human renal transplantation. Transplantation 57: 1450–1454
27. Transplant Resource Center of Maryland, Organ Donation Committee proposal by Drs. Dilip Kittur and James Burdick