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# COLD ISCHEMIA AND OUTCOME IN 17,937 CADAVERIC KIDNEY TRANSPLANTS[1,2]

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**To determine if cold preservation time continues to affect renal transplant outcome, prospectively collected data from 17,937 cadaveric renal transplants performed between 1982 and 1991 were analyzed. Cold preservation intervals of 1–16, 16–32, 32–48, and greater than 48 hr were studied by multi- and univariate methods for two time periods: 1982–1989 (n=13800) and 1990–1991 (n=4137). The functional one-year graft survival for kidneys stored over different intervals was significantly different ($P<0.001$) only for**

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**the 1982–1989 epoch: one-year allograft survival ranged from 76% (1–16), to 72% (16–32 and 32–48) to 74% (>48) hr. One-year graft survival ranged from 81 to 83% for the four preservation times in 1990 through 1991 ($P$=NS). Overall actuarial graft survival was 76% (74% prior to 1990, and 82% after 1990). Factors significantly ($P$<0.0001) affecting kidney transplant outcome before and after 1990 were delayed graft function (DGF): n=4232, 65% one-year graft survival; retransplant status: n=3029, 67% one-year graft survival; and HLA match at three or more loci: n=6067, 79% one-year graft survival. While DGF occurred more often with prolonged preservation, kidneys with DGF had similar survival regardless of preservation duration. Before 1990, pretransplant transfusion was associated with better and black recipient race with worse outcome; neither transfusion nor recipient race had any effect after 1990. Patients receiving kidneys preserved for longer periods demonstrate one-year graft survival comparable to kidneys preserved for shorter periods. Prolonged cold ischemic time should no longer be a principal reason for considering organ discard.**

Over 25,000 patients await cadaveric renal transplantation in America. During 1993, 4849 cadaveric donors in the United States represented a potential 9698 kidneys for transplantation (*1*). Of these, 8162 (84.1%) were transplanted, leaving 1536 kidneys, many of which were recovered but not transplanted. Kidney discard rates are increasing, and nonrecovery or discard may occur for numerous reasons, among which are anatomic abnormalities, organ contamination, prolonged cold ischemia, and donor circumstances precluding kidney recovery (*2–4*). The number of waiting patients is increasing rapidly while the number of organ donors is not (*5*). Thus, every kidney that is recovered should be used and discard must not occur unless sound reasons for wasting the kidney are evident.

While kidney sharing in the United States has been shown to be both workable and advantageous (*4–8*), transport of organs increases cold ischemic times. Longer cold ischemia has been associated with high rates of delayed graft function, which is associated with increased morbidity and is a detrimental factor to graft and patient survival (*9–12*). Certain patient populations such as military dependents or island dwellers often receive kidneys stored for prolonged periods because the patient, the organ, or both must travel long distances to the transplant center. In addition, the kidney shipped to a distant center for a specific patient may not be used, and transport to another center for the next computer-selected recipient results in even longer cold ischemia.

Despite known preservation capabilities, questions regarding extended cold ischemia and ultimate outcome in organ transplantation remain (*13–15*). In addition, the use of nephrotoxic drugs in the immediate posttransplant period compels a critical assessment of any kidney stored ex-vivo for a prolonged time (*16, 17*). To determine the impact of preservation time on renal transplant outcome, prospectively collected data from the South-Eastern Organ Procurement Foundation (SEOPF) member institutions were studied. The intent was to detect the presence or absence of any adverse effect of prolonged renal allograft ex-vivo preservation on renal allograft survival.

## MATERIALS AND METHODS

From January 1, 1982 to December 31, 1991, data on 17 daveric kidneys transplanted by the 48 SEOPF member inst were entered into the SEOPF data base. All cadaveric kidne plants performed by a SEOPF institution during this peri included. All organs were distributed through the allocati rithms of the United Network for Organ Sharing (UNC SEOPF. Each SEOPF member institution has submitted information about all transplants since June of 1977; UN collected those data since October of 1987 (*3–7*). Informatio the organ donor, the kidney, the transplant recipient, and posttransplant follow-up data enable tracking of kidneys fi point of recovery to current posttransplant outcome. The n data acquisition, computer entry, and quality control have b firmed and reported; both data bases have been used to lin circumstance and graft outcome in a number of studies multivariate statistical techniques (*2–7, 11, 12, 18, 19*).

Multivariate analyses were performed using the Cox prop hazards model (*20*). Demographic variables were compare standard chi-square methods. Covariates were considered to association with outcome when $P$<0.05, and the relative ri was >1.20 or <0.85. Life table analysis to determine patient a survival curves and the probability of difference between cu calculated by both the Breslow (generalized Wilcoxon) met the Mantel-Cox (Savage) method (*21, 22*). The former allo weight to early differences that could relate to preservation while the latter allows more weight to later differences. Cur actuarial survival was calculated using fully reported data plete reporting prompted withdrawal of the recipient from analysis.

Factors included in the Cox proportional hazards model i demographic data as well as information deemed importan come as related to the donor, the kidney, and the recipient ( Separate analyses were performed by partitioning the stu tients into those who received kidneys preserved for 1–16 h hr, 32–48 hr, and more than 48 hr. Since cold preservation University of Wisconsin solution became widespread after 1 differences in outcome related to duration of preservation be after January of 1990 were sought through a separate analy variables for those 13,800 kidneys transplanted before Ja 1990, and the 4137 kidneys transplanted in 1990 through

Donor and recipient HLA antigen profiles were linked mine grade of match. Of any six HLA A, B, and DR antigen fied, a good match was defined as antigen matching at three loci; a poor match was defined as a zero-, one-, or two-HLA match. Preservation by static cold storage or pulsatile met both) was noted. Kidney sharing meant that the organ was r by one reporting institution (transplant center or OPO) ar planted at another. Current percent panel-reactive antibo was chosen as a variable that would denote the immunolo tivity of the patient at the time of transplantation; sha among SEOPF centers allowed for a preliminary crossmatc rent (one-month-old) sera prior to shipping a kidney. Dela function was defined as dialysis during the first postgraft

TABLE 1. Data analyzed in 17,937 cadaveric renal trans

| Donor/kidney | Recipient |
|---|---|
| Age/race/gender | Age/race/gender |
| HLA profile | HLA profile |
| Multiorgan donor: yes/no | Regraft: yes/no |
| Preservation method: pulsatile/static/combination | Prior transfusion: yes/no |
| | Panel-reactive antibody >6 |
| Duration of preservation (hr): 1–16; 16–32; 32–48; >48 | Dialysis first postgraft wee |
| | Graft survival |

the entire 17,937 kidneys, 11,291 (63%) were transplanted in 10,938 (61%) in white recipients, and 3029 (17%) in patients previously received a kidney transplant. An HLA match at or more loci (good) occurred in 6067 (34%) transplants. A cur-RA greater than 60% was reported in 927 (5%) recipients. were 872 (5%) kidneys from donors age 55 years or greater. d graft function occurred in 4232 (24%) of the entire study tion. Only 1034 kidneys (6%) were preserved only by pulsatile vation methods.

## RESULTS

length of cold preservation time of transplanted cadaveric s was not a factor determining one-year graft survival in transplantation (Table 2). Kidneys preserved for more 8 hr had one-year allograft survivals similar to those of all s preserved for shorter periods in each epoch. Graft func- survival for kidneys stored 1–16 hours was better than preserved for longer periods before 1990 ($P<0.001$)— er, the 16–32, 32–48, and more than 48 hr groups demon- similar survival at one year in the 1982–1989 epoch. In 990–1991 epoch, one-year allograft survival was not de- nt upon duration of kidney preservation, and a higher tage of kidneys survived at one year than the 1982–1989 For the 13,800 grafts transplanted before 1990, one-year rial graft survival was 74%; for those 4137 transplanted in nd 1991, one-year actuarial graft survival was 83%. For 937 kidneys, one-year actuarial graft survival was 76%.

strength of association and magnitude of effect on transplant outcome for each covariate demonstrating tical significance (Cox model) is summarized in Table 3. rs with the strongest association were delayed graft on, degree of match, retransplanted recipient, black nd prior transfusion for all kidneys transplanted dur- entire 10-year period and for those transplanted prior 0. During 1990 and 1991, however, the outcome for kidneys studied was most significantly associated with d graft function and degree of match at the $P<0.0001$ Combined pulsatile-static preservation ($P<0.003$), and splantation ($P<0.02$) adversely affected outcome. Do- ace and gender were associated with a significant $P$ and risk ratio only in the 1990 to 1991 epoch. Similar r reports (*5*, *7*), a greater number of white (3706; 80%) (2650; 64%) donors existed, but no particular clinical ne pattern could be determined due only to donor race der and preservation duration in univariate analysis. g the 1990–1991 period, the previously significant vari- of recipient race and transfusion status had no demon- e effect. Variables never affecting outcome included or- sharing, multiorgan recovery, recipient age, and nt gender. The older donor organ and recipient sensi- n with PRA>60% were associated with poorer outcome (univariate analysis only) in both epochs than overall outcome. Analyzed as covariates in the Cox model, none of the four categories of cold ischemia time influenced graft outcome.

Delayed graft function occurred significantly more often in kidneys preserved beyond 16 hr (Table 4). The 4232 kidneys having delayed allograft function demonstrated worse actuarial one-year graft survival than those 13,705 organs with immediate function (65% versus 79%; $P<0.0001$). Delayed function was detrimental at all preservation times and in each of the two epochs reviewed (Table 5). One-year allograft survival, however, was not related to the duration of organ preservation when delayed graft function occurred. In neither epoch could delayed graft function be found to more adversely affect the kidney stored for a longer period as compared with an organ transplanted with a shorter cold storage time but still affected by delayed allograft function.

The 6067 patients matched at three or more HLA loci had a 79% graft survival at one year compared with 74% for the 11,870 kidneys matched at two or fewer HLA loci ($P<0.0001$). Patients were more likely to have a good donor-recipient match (three or more HLA A, B, DR antigens) when receiving shared grafts regardless of preservation time ($P<0.001$). The proportions of patients receiving shared, well-matched grafts for each of the four preservation periods were: 1–16 hours, 40%; 16–32 hr, 50%; 32–48 hr, 43%; and beyond 48 hr, 41%. Locally procured and transplanted kidneys demonstrated good HLA match in 27% of cases, and this proportion did not vary with different preservation times. Preservation time was not the sole factor affecting outcome in either poorly or well-matched kidney transplants (Table 5).

For the 3029 retransplanted patients, one-year graft survival of 67% was worse ($P<0.0001$) than the 77% one-year graft survival in primary transplantation. Preservation time, however, had no demonstrable effect on retransplant outcome (Table 5). In the 1990–1991 era, the 13 kidneys preserved for more than 48 hr could not be evaluated by actuarial methods beyond five months. The 88% actuarial one-year allograft survival for the 85 kidneys preserved from 32–48 hr was not worse for retransplant recipients than for kidneys preserved for less than 32 hr.

Actuarial one-year renal allograft survival for 5743 black transplant recipients was not dependent upon the length of cold kidney preservation either before or after January 1990 (Table 5). Prior to 1990, one-year actuarial graft survival ranged from 68% to 73% (72% for grafts preserved beyond 48 hr), and in 1990 and 1991 graft survival ranged from 81% to 83% (82% for grafts stored more than 48 hr). While 70% one-year actuarial graft survival for 4423 black patients in the 1982–1989 epoch was below the 74% experienced for all patients, actuarial graft survival (82%) in 1320 black recipients transplanted in 1990 and 1991 was not practically different from that of all patients (83%) during those two years.

Donor age over 55 years (872 kidneys) and recipient panel reactive antibody >60% (927 patients) were not significant factors in multivariate analysis, although each was associated with diminished one-year allograft survival as determined by univariate calculations (Table 5). When compared with short cold ischemia time, longer preservation times for kidneys from older donors or for kidneys transplanted to sensitized patients did not result in worse one-year graft survival.

2. 17,937 Renal allografts and percent one-year actuarial survival by preservation time—1982–1989 and 1990–1991

| vation (hr) | 1982–1989 | | 1990–1991 | |
|---|---|---|---|---|
| | Number | % Survival | Number | % Survival |
| 16 | 5398 | 76 | 1643 | 83 |
| 32 | 6078 | 72 | 1788 | 82 |
| 48 | 1988 | 72 | 614 | 83 |
| 48 | 13,464 | 74 | 4045 | 83 |
| 48 | 336 | 74 | 92 | 81 |
| All | 13,800 | 74 | 4137 | 83 |

TABLE 3. Multivariate analysis of factors associated with renal allograft outcome

| Variable | Parameter estimate | Standard error | PR> (chi-square) | Ris rati |
|---|---|---|---|---|
| 1982–1991 (17,937 transplants) | | | | |
| Delayed function | 0.47 | 0.027 | 0.0001 | 1.5 |
| Match | −0.20 | 0.027 | 0.0001 | 0.8 |
| Retransplant | 0.30 | 0.030 | 0.0001 | 1.3 |
| Recipient race | 0.20 | 0.025 | 0.0001 | 1.2 |
| Pre-TX transfusions | −0.24 | 0.030 | 0.0001 | 0.7 |
| Preservation method | 0.01 | 0.018 | 0.5584 | 1.0 |
| Cold ischemia time | 0.02 | 0.017 | 0.2296 | 1.0 |
| 1982–1989 (13,800 transplants) | | | | |
| Delayed function | 0.04 | 0.029 | 0.0001 | 1.4 |
| Match | −0.17 | 0.029 | 0.0001 | 0.8 |
| Retransplant | 0.30 | 0.032 | 0.0001 | 1.3 |
| Recipient race | 0.23 | 0.027 | 0.0001 | 1.2 |
| Pre-TX transfusions | −0.23 | 0.030 | 0.0001 | 0.7 |
| Preservation method | 0.02 | 0.019 | 0.2506 | 1.0 |
| Cold ischemia time | 0.01 | 0.020 | 0.4572 | 1.0 |
| 1990–1991 4,137 transplants | | | | |
| Delayed function | 0.84 | 0.068 | 0.0001 | 2.3 |
| Match | −0.29 | 0.069 | 0.0001 | 0.7 |
| Retransplant | 0.22 | 0.089 | 0.0141 | 1.2 |
| Recipient race | 0.53 | 0.067 | 0.4284 | 1.0 |
| Donor gender | −0.18 | 0.067 | 0.0064 | 0.8 |
| Donor race | 0.19 | 0.088 | 0.0291 | 1.2 |
| Pre-TX transfusions | 0.05 | 0.066 | 0.4071 | 1.0 |
| Preservation method | 0.29 | 0.091 | 0.0023 | 1.3 |
| Cold ischemia time | 0.02 | 0.043 | 0.6818 | 1.0 |

TABLE 4. Number of renal allografts and percent having delayed graft function (DGF) by preservation time for 17,937 kidneys

| Preservation time hr | Transplant occurring 1982–1989 | | | Transplant occurring 1990–1991 | | |
|---|---|---|---|---|---|---|
| | n | No. DGF | %DGF[a] | n | No. DGF | %DGF[b] |
| 1–16 | 5398 | 1152 | 21 | 1643 | 348 | 21 |
| 16–32 | 6078 | 1471 | 24 | 1788 | 432 | 24 |
| 32–48 | 1988 | 551 | 28 | 614 | 158 | 26 |
| >48 | 336 | 90 | 27 | 92 | 30 | 33 |
| All | 13,800 | 3264 | 24 | 4137 | 968 | 23 |

[a] $P<0.001$ DGF occurring at different preservation intervals.
[b] $P<0.006$ DGF occurring at different preservation intervals.

## DISCUSSION

The judgement to accept a cadaveric kidney for transplantation to a particular patient utilizes information related to the donor, the organ, cold ischemia preservation status, and the recipient. An important feature in the clinical decision process has been duration of donor organ preservation (*2, 4, 8, 9, 13–17, 19*). Further, the length of preservation time may be perceived as affecting some circumstances more than others (*5*). For example, a transplant center might be positively inclined to accept a kidney preserved 48 hr or more if the kidney came from a young donor and was an excellent HLA match with the intended recipient. Other considerations would, of course, influence judgement, but the clinical presentation of a donor kidney incites questions in the receiving-transplanting institution related to a number of factors. This review of 17,937 kidneys disclosed that prolonged preservation time had no effect on one-year graft survival when multivariate analysis included a number of donor, preservation, and recipient factors. This was particularly true for the era of 1990–1991, when both static and pulsatile preservation techniques employed modern preservation solutions—mainly the University of Wisconsin solution.

Preservation times of 1–16, 16–32, 32–48, and more than 48 hr did not affect one-year actuarial graft survival v data were analyzed by univariate methods (Table 5). within the categories of kidneys from donors over 55 yea age, black recipient race, and the retransplant circumst longer organ preservation times could not be shown t versely affect one-year actuarial allograft survival. Su result is supported by prior analyses disclosing no addit adverse interaction of prolonged cold ischemia and dono or retransplant status (*5, 7, 23*). Well known to a recip transplanting institution at the time any kidney is off these variables (i.e., older donor, black recipient, retr plant) may not be important at least insofar as a sp effect of extended preservation of kidneys is concerned. lower one-year actuarial graft survivals for patients rece kidneys from older donors and for retransplant patient supported by other studies (*5, 7, 8, 23, 24*). The 1320 recipients in 1990–1991 had renal allograft outcomes sir to all patients, a new and welcome circumstance.

Considerable study has related renal allograft outcor delayed graft function due, at least partly, to the durati cold kidney ischemic time (*2, 8–13, 24, 25*). The use of r rotoxic drugs (including immunosuppressants) is spread, and nephrotoxicity may exacerbate a number o

TABLE 5. Number of renal transplants by category and percent actuarial graft survival at one year

| Preservation time (hr) | Delayed function | | HLA antigen match | | | | Retransplant recipient | | Black recipient | | Donor age >55 | | PRA >60% | | All | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 0–2 | | 3–6 | | | | | | | | | | | |
| | n | % | n | % | n | % | n | % | n | % | n | % | n | % | n | % |
| 1982–1989: | | | | | | | | | | | | | | | | |
| All | 3264 | 64 | 9280 | 72 | 4520 | 77 | 2462 | 65 | 4423 | 70 | 537 | 70 | 772 | 67 | 13800 | 74 |
| 1–16 | 1152 | 64 | 3851 | 74 | 1547 | 80 | 926 | 67 | 1443 | 73 | 225 | 71 | 290 | 68 | 5398 | 76 |
| 16–32 | 1471 | 64 | 3957 | 71 | 2121 | 76 | 1150 | 63 | 2177 | 68 | 239 | 67 | 354 | 64 | 6078 | 72 |
| 32–48 | 551 | 64 | 1249 | 70 | 739 | 75 | 331 | 65 | 692 | 70 | 85 | 71 | 113 | 70 | 1988 | 72 |
| >48 | 90 | 65 | 223 | 73 | 113 | 75 | 55 | 62 | 111 | 72 | 8 | NC[a] | 15 | 60[b] | 336 | 74 |
| 1990–1991: | | | | | | | | | | | | | | | | |
| All | 968 | 69 | 2590 | 81 | 1547 | 85 | 567 | 79 | 1320 | 82 | 335 | 75 | 155 | 75 | 4137 | 83 |
| 1–16 | 348 | 65 | 1069 | 82 | 574 | 85 | 219 | 80 | 476 | 83 | 100 | 75 | 160 | 73 | 1643 | 83 |
| 16–32 | 432 | 69 | 1086 | 80 | 702 | 85 | 250 | 74 | 594 | 81 | 174 | 74 | 65 | 72 | 1788 | 82 |
| 32–48 | 158 | 74 | 388 | 83 | 226 | 85 | 85 | 88 | 225 | 81 | 53 | 76 | 25 | 75 | 614 | 83 |
| >48 | 30 | 76[b] | 47 | 77 | 45 | 83 | 13 | 77[b] | 25 | 82 | 8 | NC[a] | 5 | NC[a] | 92 | 81 |

[a] NC = data not sufficient for calculation.
[b] Survival at five months; 12-month data NC.

rs in the early posttransplant period (*16, 17, 26*). In ddition, large volumes of intravenous fluid given at the time f transplant surgery may lead to a need for dialysis within he first posttransplant week unless excellent early graft nction occurs. This definition of delayed graft function (i.e., he need for dialysis in the first postgraft week) may need to e questioned. Many patients requiring a single or even a econd dialysis treatment within one week of transplantation ay not have a significantly dysfunctional kidney (*28*). For he 17,937 kidneys herein reported, delayed graft function as noted in 21% to 33% of transplants, a rate similar to that eported elsewhere (*23, 27, 28*), and delayed function did ccur more frequently in kidneys preserved for a longer time. urther, allograft survival was worse when delayed graft nction was noted. However, when delayed graft function ccurred, it did not more adversely affect kidneys preserved r extended periods than it did kidneys preserved for 1 to 16 r 16 to 32 hr. In fact, in the more modern epoch of 1990 to 991, all kidneys preserved beyond 32 hr and demonstrating elayed graft function did somewhat better than kidneys ith delayed graft function transplanted before 32 hr of cold chemia time. This may mean that delayed allograft func- on is a multifactoral clinical circumstance related to pres- rvation time, but also related to a number of other factors (*8, , 15, 24, 25, 28*). Further, grafts demonstrating severe dys- nction may be lost from unsuspected immunologic rather an preservation events (*29*).

In the early 1980s SEOPF arranged for overseas use of ose kidneys not accepted by any United States transplant nter. A principal receiving institution was the Turkish ansplantation and Burn Foundation of Ankara, Turkey. In report to SEOPF (*10*), that center gave details of 100 kid- ys transplanted in 1983; 96 of the grafts had cold static eservation times of 48 to 108 (mean 69) hr. The preserva- n times for the other four kidneys were 24 to 44 (mean 37) The principal preservation solution was Euro-Collins. ne kidneys had primary nonfunction, and 87 grafts ulti- tely functioned, 80 of these for one month or more. Post- nsplant dialysis was required in 80% of cases, so early sfunction was the rule; cyclosporine was given to only one patient, a recipient of a primary nonfunction kidney. Thus, by 1983, a cooperative international kidney sharing arrangement had demonstrated the functional potential of human cadaveric kidneys following very long cold preservation. Others have reported functional results with longer cold ischemia times not different from outcomes when preservation times were shorter (*5, 7, 23, 25*).

Results in renal transplantation have improved markedly over the last decade, with cadaveric graft survival of over 80% in many centers (*2–8, 11, 13, 23–30*). Newer immunosuppressive methods, better crossmatch techniques, and improved solid organ preservation have all contributed to this generally better outcome. That numerous variables continue to impact renal allograft survival, however, is expected, but prolonged cold ischemia is not similar to most other variables. Time passes inexorably without regard to donor, kidney, and recipient circumstances that do not change. Thus, in the decision to accept a kidney that has been ex-vivo for 24 hr, a surgeon suspects that revascularization before 36 hr is unlikely, and that cold ischemia time approaching 48 hr could be expected. Clearly, data reported herein document that functional viability of kidneys preserved to and beyond 48 hr may be expected with modern preservation methods.

During 1993, over 1500 kidneys from cadaveric donors were not recovered or were discarded following recovery and the intent to preserve and transplant the organ. A contributing reason for not using some of these organs was likely prolonged cold ischemic time. Data analysis of the 17,937 kidneys herein reviewed confirms some already documented predictors of bad or good outcome. Graft survival was adversely affected by recipient retransplant, poor match, and delayed graft function. Good outcome was more likely to occur in primary allograft recipients who received a well-matched organ with immediate graft function. Sharing of kidneys and duration of preservation did not adversely affect outcome. Kidneys preserved beyond 48 hr demonstrated functional one-year allograft survival not different from organs preserved for shorter periods. Kidneys preserved for prolonged periods should no longer be discarded for that reason alone.

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