Prediction of Renal Transplant Survival from Early Postoperative Radioisotope Studies

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It has been routine at the University of Alabama Medical Center to obtain a radionuclide renal function study immediately after transplantation (usually within 3 d) that includes estimation of effective renal plasma flow (ERPF) from a single plasma sample in addition to imaging. We present here the correlation between baseline measurements and the 1-y graft survival. **Methods:** Two cohort years were reviewed: 1988, when ^{131}I-orthoiodohippurate (OIH) was used; and 1995, when ^{99m}Tc-mercaptoacetyltriglycine (MAG3) was used. ERPF was measured concurrently with gamma-camera imaging by previously published single-injection, single-sample methods (converting MAG3 clearance to ERPF by means of a correction factor). **Results:** Graft survival during the first postoperative year improved significantly in the interval between cohort years, from 74% of 147 cadaver (CD) grafts in 1988 to 91% of 200 CD grafts in 1995 (log rank test, $P < 0.05$). In contrast, for living related donor (LRD) grafts there was no significant change, from 91% of 66 in 1988 to 91% of 83 in 1995. The baseline ERPF was a significant predictor of graft survival in both 1988 and 1995 (Wilcoxon test, $P > 0.05$). For LRD grafts the association was not significant in either year. Using MAG3 (1995), the peak time and the ratio of counting rate (R) at 20 min to that at 3 min (R20:3) were also significant predictors for CD graft survival. Using OIH (1988 cohort), the correlation with peak time did not reach significance, and the R20:3 measurement was not available. Although multivariate combinations (Cox proportional hazards model) did not have significantly more predictive value at the 95% confidence level than ERPF or R20:3 alone, some statisticians suggest a 75% confidence level for adding an additional covariate to a multivariate model. Use of this level led to a model including both ERPF and R20:3. **Conclusion:** Single-sample ERPF measured in the immediate post-transplant period, whether from OIH clearance or MAG3 clearance, was a statistical predictor of graft survival for CD transplants. For MAG3, the peak time and R20:3 were also significant predictors. These associations held only for CD transplants and not for LRD transplants.

Key Words: kidney transplant; kidney function; acute tubular necrosis; delayed graft function

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It has been routine at the University of Alabama Medical Center to obtain a radionuclide scan immediately after transplantation (usually within 3 d), including effective renal plasma flow (ERPF) estimation from a single plasma sample (*1–9*). This protocol was initiated in 1975 using the radiopharmaceutical ^{131}I-orthoiodohippurate (OIH), which was used through 1990. In January of 1991, ^{131}I-OIH was replaced by ^{99m}Tc-mercaptoacetyltriglycine (MAG3). An empirical correction was used to convert MAG3 clearance to ERPF, but otherwise the protocol remained essentially unchanged.

The rationale for the routine quantitative baseline study is to provide a reference point to determine whether function is improving or deteriorating in the immediate post-transplantation period. Prompt recognition of changing function is of particular value for patients whose postoperative course is complicated by delayed graft function (formerly called acute tubular necrosis [ATN]), acute rejection (AR), or other problems. The time course over repeated radionuclide studies serves to distinguish ATN (present at baseline and improving) from AR (delayed onset and deteriorating), 2 entities that are hard to distinguish from each other on a single study.

Although the purpose of these tests was to aid in immediate postoperative management, we have noted an association with long-term prognosis. In this article we evaluate statistically the relationship between the initial postoperative baseline measurements and 1-y graft survival in 2 distinct cohort years: 1988, when OIH was used; and 1995, when the newer agent MAG3 was used.

MATERIALS AND METHODS

Data were obtained from the renal transplant registry and the nuclear medicine division at University of Alabama. Two representative years were selected for chart review and manual data entry, 1 before and 1 after the introduction of the radiopharmaceutical MAG3. Two cohort years were analyzed, 1 when ^{131}I-OIH was used as the imaging agent and 1 when ^{99m}Tc-MAG3 was used. The management protocol mandated radionuclide scans in the immediate postoperative period for all renal transplant recipients. Because of clinical instability, nuclear medicine studies were not performed within the first 4 postoperative days on 5 of the 218 transplants (2.3%) done in 1988 and 16 of the 301 (5.2%) done in 1995. In 1995, measurements on 2 patients (0.7%) were technically unsuccessful. Results from all patients for whom data are available provide the basis of this study, 213 in 1988 (97.7%) and 283 in 1995 (94.0%). Because the objective was to interpret the significance of the radionuclide measurements of renal function, only

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those subjects who had successful radionuclide studies were included in the statistical analysis, and deaths of patients with functioning grafts were treated as censored at the date of death.

Immunosuppressive Protocols

Recipients in both years received quadruple immunosuppressive prophylaxis, with antibody induction (*10*). In 1988, standard therapy consisted of preoperative doses of Minnesota antilymphoblast globulin (MALG), azathioprine, and methylprednisolone. After acceptable allograft function was established, cyclosporine was instituted at 8–10 mg/kg/d. After 7–14 d, the MALG was discontinued, and the patient was maintained long term on cyclosporine, azathioprine, and prednisone. In 1995, Orthoclone OKT3 was used instead of MALG. After August of 1995, mycophenolate mofetil was substituted for azathioprine. In both cohorts, baseline ERPF studies were performed in the absence of cyclosporine, a potential complicating variable (*11*). Episodes of acute rejection in both periods were diagnosed by isotope renography, percutaneous biopsy, or both, and treated initially with high-dose corticosteroids; additional antibody administration was reserved for those recipients with steroid-resistant rejection. In both periods, cadaver (CD) kidneys were preserved between harvesting and engraftment with pulsatile perfusion.

Nuclear Medicine Procedures

The radionuclide examination included an imaging study combined with ERPF estimation from a single blood sample. Peak times were measured as the time interval from tracer administration to maximum background-corrected counting rate (R). A region of interest was used that included the whole kidney. For background correction, the background region of interest was a ring surrounding the kidney. The ratio of R at 20 min to that at 3 min (R20:3) was measured from a background-corrected region of interest covering the whole kidney using 1-min time intervals ending at 20 and 3 min (*12*). The ERPF was calculated from a single plasma sample obtained at a fixed time after tracer administration using an empirical formula appropriate to OIH or MAG3 (*5,6,8,9*). ERPF values and peak times were recorded in both 1988 and 1995, but the R20:3 was recorded only in 1995.

At this clinic the radiopharmaceutical ^{131}I-OIH was used from 1977 to 1990, and ^{99m}Tc-MAG3 has been used from 1991 to the present. Although ERPF is conventionally defined as para-aminohippurate (PAH) clearance, a close correlation has been shown between PAH clearance and OIH clearance (correction factor, ~0.90) (*13*). OIH clearance is in turn closely correlated with MAG3 clearance (correction factor, ~0.59) (*5,7,8*). The correction from MAG3 clearance to ERPF is thus the product of both factors, 0.90 and 0.59, with the result 0.53. (Direct comparison of clearance between PAH and MAG3 has not been reported.) We have routinely reported both OIH clearance and MAG3 clearance in units of estimated ERPF, which has enabled us to maintain continuity of the database despite the change in agents. For MAG3, either the above conversion factor or a formula that gives ERPF directly from plasma MAG3 concentration was used (*5*). For OIH, the formula of Tauxe et al. (*14*) was used, which yields results about 10% higher than true OIH clearance, compensating for the difference in extraction fraction between OIH and PAH (*6*). Gamma-camera images of the injection site were obtained routinely, and only measurements without evidence of extravasation were accepted as valid.

RESULTS

Overall 1-y graft survival data are shown in Table 1. Note that the graft survival improved significantly between cohort years 1988 and 1995, presumably because of advances in treatment during the interim. In contrast, for living related donor (LRD) grafts, there was no significant change between 1988 and 1995.

The correlation of CD graft survival with renographic parameters is presented in Table 2. (The corresponding statistics were also calculated for LRD grafts, but because none of the associations were significant or approached significance, the results are not shown.) All data were treated as statistically censored at 365 d after transplantation. Deaths within 365 d that occurred with a functioning graft were treated as censored at the time of death. Table 2 shows the relationship of CD graft survival to baseline ERPF, peak time, and (for 1995 only) the R20:3. The baseline ERPF was a significant predictor of graft survival in both 1988 and 1995, both by the Wilcoxon rank sum test (ranking the baseline ERPF for the 2 groups consisting of 1-y surviving and nonsurviving grafts) and by the univariate Cox proportional hazards model (censored at the end of the first postoperative year). Despite the smaller number of failures in 1995, which effectively reduced the sample size and made it harder to show statistical significance, and despite the differences in management responsible for improved graft survival, the association was still significant in 1995. For peak time, the association was weaker, attaining significance for the Cox model only in 1995, when MAG3 was in use, but approaching significance in 1988. The R20:3 was a significant predictor of 1-y graft survival in 1995 but was not measured in 1988.

Corresponding statistics were also calculated for LRD grafts. In contrast to the findings for CD grafts, none of the variables proved to be significant predictors of 1-y graft survival. Thus, the predictors of survival identified above are valid only for CD grafts.

Table 3 shows results of the Cox model for multivariate combinations of the renographic parameters for CD grafts in 1995, when the R20:3 measurement was available. The first

TABLE 1
Graft Survival in 1988 and 1995

Parameter	CD grafts		LRD grafts	
	1988	1995	1988	1995
Agent	OIH	MAG3	OIH	MAG3
Total no.	147	200	66	83
1-y graft survival (%)	74	91	91	91
Functioning graft (no.)	104	174	58	74
Failed graft (no.)	36	17	6	7
Patient died with functioning graft (no.)	7	9	2	2

LRD = living related donor.

TABLE 2
CD Graft Survival Versus Renographic Parameters

Parameter	1988	1995
Agent	OIH	MAG3
Total no.	146	200
1-y graft survival (%)	74	91
Functioning graft (no.)	103	174
Failed graft (no.)	36	17
Patient died with functioning graft (no.)	7	9
ERPF		
Wilcoxon z	−2.52	−2.25
Cox z	−2.34	−2.52
Relative risk*	1.50 (1.08–2.08)	2.3 (1.2–4.5)
Survivors (mean ± SD)	274 ± 14	254 ± 8
Failed (mean ± SD)	214 ± 20	191 ± 18
Peak time		
Wilcoxon z	1.43	1.97
Cox z	1.57	2.21
Relative risk*	1.03 (1.00–1.07)	1.06 (1.01–1.1)
Survivors (mean ± SD)	13.9 ± 1.1	11.9 ± 0.7
Nonsurvivors (mean ± SD)	16.5 ± 1.7	17.5 ± 2.5
R20:3		
Wilcoxon z		2.2
Cox z		2.72
Relative risk*		2.0 (1.2–3.4)
Survivors (mean ± SD)		1.12 ± 0.06
Failed (mean ± SD)		1.53 ± 0.21

*Range in parentheses.

3 rows show single-covariate fits, and the next 3 rows show 2-covariate fits. In examining Table 3, recall that significance at the 95% confidence level corresponds to a z value of ~2.0. At this confidence level, only the univariate combinations are significant. However, once a significant univariate relationship has been shown, some statisticians suggest that additional covariates should be included in a multivariate model if the incremental improvement is significant even at the 75% level (*15*). The 75% significance level corresponds to a z value of ~1.0. By this criterion, Table 3 shows that a combination of ERPF and R20:3 should be selected. This combination maximizes the log likelihood and also corresponds to our usual clinical interpretation of these measurements. Using this combination, the estimated risk of failure increased by a factor of 1.9 for each fall of 100 mL/min in ERPF and increased by a factor of 1.6 for each rise of 1 unit in R20:3.

TABLE 3
Univariate and Pairwise Combinations of Renographic Parameters for CD Grafts in 1995

Log likelihood	z*		
	ERPF	R20:3	Peak time
Univariate			
−85.08	−2.5		
−85.87		2.7	
−86.57			2.2
Pairwise			
−84.01	−1.8	1.5	
−84.62	−1.9		0.9
−85.75		0.5	1.3

*Standard normal variate z (Wald test) for graft survival in Cox proportional hazards model.

The association between renographic parameters and graft survival is illustrated by the survival curves in Figures 1 and 2. The thresholds chosen for ERPF and R20:3 were selected to achieve best separation of the survival curves to illustrate the differences shown above by more sensitive threshold-free statistical tests.

The association between the baseline measurements and the clinical diagnosis of ATN is shown in Figure 3 for cohort year 1995 using MAG3. In the transplant database, patients were defined as having ATN if they required dialysis in the first week after transplantation. Observe that R20:3 was above the normal limit of 0.8 (*12*) in every case with the clinical classification ATN and that the ERPF was below the normal limit of 250 mL/min in every instance but 2. (By the criteria used in the nuclear medicine clinic, most of the patients with low ERPF and high R20:3 were assigned a diagnosis of ATN, but in the clinical classification used for the transplant database, only those cases severe enough to require dialysis in the first week were so classified.) The association with the clinical diagnosis of ATN was strong for both R20:3 (Wilcoxon rank sum, $P < 0.001$) and ERPF ($P < 0.001$). A very similar plot was shown in our 1975 report, in which excretory index was used instead of R20:3 and OIH was used instead of MAG3.

DISCUSSION

Although many different numeric parameters have been used to describe renographic time–activity curves, these parameters can generally be divided into 2 classes corresponding to either the height or the width of the curve. One

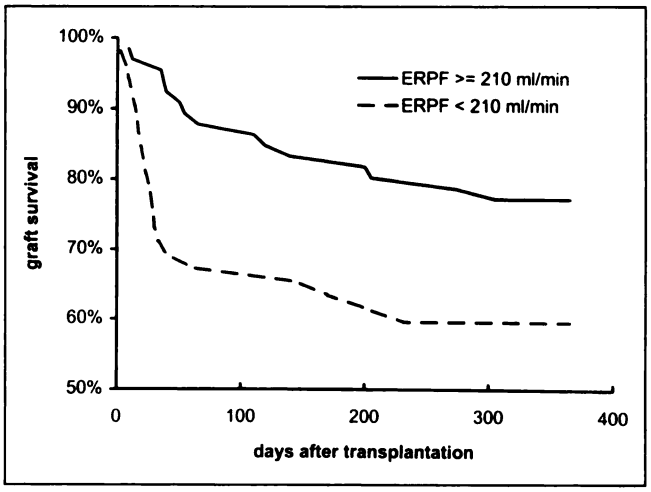

FIGURE 1. Dependence of CD graft survival on baseline ERPF in 1988 (using OIH as radiopharmaceutical).

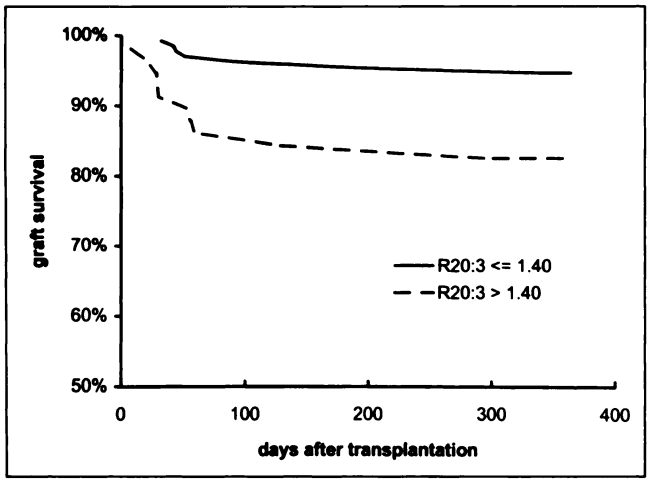

FIGURE 2. Dependence of CD graft survival on baseline ERPF in 1995 (using MAG3 as radiopharmaceutical).

class measures the height of the time–activity curve, reflects tracer uptake, and has dimensions of activity or R. The other class measures the width of the peak, reflects tracer retention, and has dimensions of time. More accurate parameters can be obtained if the external measurement of renal activity is augmented by laboratory measurement of blood and urine, as done at this center. In this work we used ERPF as the measure of tracer uptake and either peak time or R20:3 as the measure of retention.

A pattern of changes in these parameters reflecting both reduced tubular excretion and prolonged transit of tracer was shown to predict graft survival. The same pattern has long been recognized as characteristic of ATN. In 1975 we described this pattern using excretory index (EI) instead of R20:3 as the measure of retention (*1*). When seen in the immediate post-transplantation period, the pattern is highly specific for ATN, although later in the hospital course it can

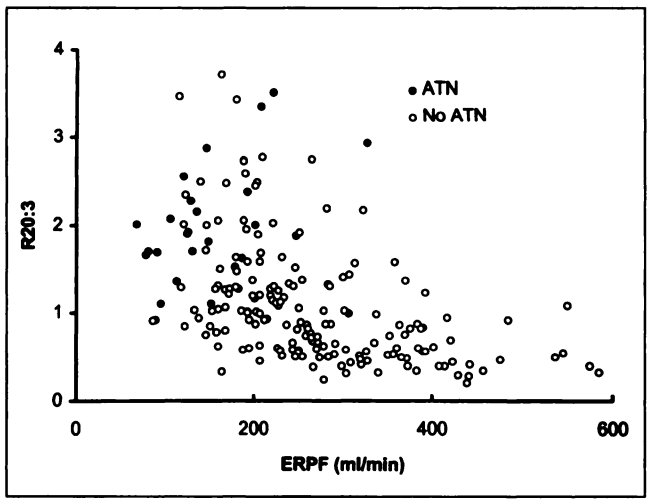

FIGURE 3. Clinical diagnosis of ATN (defined as requiring dialysis within 1 wk of transplantation) versus baseline ERPF and R20:3 (CD recipients only; cohort year 1995). Note that clinical diagnosis of ATN was associated with low ERPF and high R20:3.

be also seen in AR. The time course in sequential studies distinguishes AR from ATN. ATN typically causes glomerular filtration rate to fall more than ERPF, with a fall in filtration fraction and in urine flow. When tubular tracers such as OIH or MAG3 are used, tracer uptake is preserved but urine flow and tracer washout are impaired, leading to abnormal parenchymal retention that is easily recognized on gamma-camera images.

Although our diagnostic criteria have remained essentially the same since 1975, there have been 2 major changes in technique: replacement of OIH by MAG3 and replacement or supplementation of the EI by R20:3. After developing methods of measurement for MAG3 and showing that they correlated closely with the corresponding measurements for OIH (*5*), we changed from OIH to MAG3 in 1991. Shortly thereafter, in 1993, the parameter R20:3 was introduced as an alternate measure of retention that, unlike EI, required no urine collection or wet laboratory procedures (*12*).

The nuclear medicine findings in this study that are predictive of poor graft survival correspond to longstanding criteria for the renographic diagnosis of ATN (*1,12*). Current clinical data indicate that delayed allograft function is highly correlated with adverse outcomes in renal transplantation. Thus, the reason these findings predict graft survival may be their reliability as an early quantitative index of ATN. Because ATN is an infrequent complication of LRD transplantation, this relationship may also explain why the association between ERPF, ATN, and outcome was found only for recipients of CD grafts. Alternatively, baseline ERPF may also be a proxy for functioning renal mass, another important variable influencing graft survival. Remaining to be clarified by further study are the extent to which these findings can be integrated with other predictors of graft survival, associated with specific immunosuppressive regimens and used in selecting appropriate therapy.

CONCLUSION

Single-sample ERPF measured in the immediate post-transplantation period, whether from OIH clearance or MAG3 clearance, was a statistical predictor of 1-y graft survival for CD transplants. For MAG3, significant associations were also found for peak time and R20:3. The tests were predictive of graft survival only for CD transplants, and not for LRD transplants.

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