COMPREHENSIVE EVALUATION OF RENAL FUNCTION IN THE TRANSPLANTED KIDNEY

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By means of a comprehensive renal function test based on the analysis of orthoiodohippurate kinetics carried out 223 times in 86 renal transplant patients, we have been able to separate clearly five clinical entities: normally functioning transplanted kidneys, acute tubular necrosis, cell-mediated rejection, humoral (chronic) rejection, and postrenal obstruction. Accurate prediction of the fate of the rejecting kidney can be made while still subclinical as much as a week before manifestations by other techniques are evident. Data on 22 donors studied 44 times are also presented. The comprehensive test consists of measurements of effective renal plasma flow (ERPF), sequential scintigraphy, calculations of excretory index (EI) (percent dose actually found in bladder and voided urine as a fraction of the percent dose expected at a given time after injection at the patient's specific ERPF), and residual urine volume. Formulas and regression equations for the calculation of ERPF, EI, residual urine, etc., are presented.

The transplanted kidney is subjected to a variety of immunologic, vascular, and obstructive processes, each of which may require a different form of specific therapy. Unfortunately most conventional diagnostic procedures do not adequately identify these processes in the earliest stages. Several nuclear medicine studies have been suggested as valuable diagnostic aids in the evaluation of the functional status of the transplanted kidney (*1–5*).

This paper presents our results from the use of a comprehensive nuclear medicine renal function procedure (CRFP) that appears to identify accurately the major complications in recipients early in the course of the process (*6,7*). Since some post-transplantation problems may result from donor-related factors, we also present data on the donors.

MATERIALS AND METHODS

Selection of subjects. *Donors.* Forty-four studies were carried out in 22 living related donors according to the protocol presented below. The CRFP was performed in the donor usually 2 days prior to nephrectomy after renal arteriography and excretory urography had been completed. Five to seven days after surgery, the donors' effective renal plasma flow (ERPF) and excretory index (EI) described below were estimated and compared with his preoperative values and with the values in the recipient after transplantation.

Recipients. A total of 223 CRFPs were carried out in 86 recent adult kidney recipients (59 males and 27 females) at the University of Alabama Medical Center. The protocol included: (A) three measurements of ERPF and EI during the first 24 hr after surgery; (B) CRFP carried out postoperatively on Days 5, 12, and 19 unless it seemed clinically indicated to perform them earlier or at more frequent intervals; and (C) CRFP carried out at 6–60 months after transplantation. Transplant patients were grouped as normally functioning (NF), acute or chronic rejection (AR,CR), acute tubular necrosis (ATN), and postrenal obstruction, and the findings correlated with the clinical status of the patient, plasma creatinine and blood urea nitrogen concentrations, and the results of other studies including excretory urography, renal arteriography, ultrasound examination, and renal biopsies. Several patients demonstrated multiple problems such as impending rejection accompanied by incomplete obstruction or acute tubular necrosis and acute rejection. Most of the patients experienced one or more periods of rejection that were managed by treatment schemes

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consisting of high-dose prednisone and immunosuppressive drug therapy, antilymphocytic serum administration, and x-irradiation of the transplant.

Techniques. The CRFP consists of several studies carried out concurrently.

(A) An angiographic perfusion study was performed using 1 mCi of ^{99m}Tc-diethylenetriaminepentaacetic acid (DTPA) with the transplanted patient in the supine position and the scintillation camera detector positioned so that the bifurcation of the aorta, iliac arteries, and urinary bladder in addition to the kidney appeared in the camera field. The donors were studied in the prone position with the detectors placed so that both kidneys were in the field of view. Cameras used were either the Searle Radiographics Pho/Gamma III and videotape or the Picker Dynacamera/Omnicamera with FM tape attachment and fitted with collimators designed for 364 keV. Three-second sequential exposures were obtained as long as the activity was clearly localized in the arterial system and kidney. This was followed by a 40-sec "static" image to evaluate renal size and shape. Subsequently, activity was quantitated over the individual kidney(s) and bladder by the use of either the split crystal or region-of-interest mode.

(B) The renal function portion of the study was more complex and included ^{131}I-labeled orthoiodohippurate (OIH) imaging as well as precisely timed blood and urine sampling. Only OIH containing less than 1.5% free iodide as determined chromatographically by the method of Burbank, et al (*8*) was used. The renographic and urinary bladder activity curves were registered on an accurately calibrated dual-channel strip recorder attached to the output of either opposite halves of the crystal or preselected areas of interest. The urine collection period began with the intravenous injection of 150 μCi of ^{131}I-OIH in patients with one kidney (half of the standard adult dose), after which ten sequential 3-min scintigrams were obtained. Subsequently, "prevoid" bladder counts were obtained in the manual mode and the patient instructed to void at 35 min after injection. Voiding time and volume were precisely noted and ended the interval for dose and urine volume calculations. The patient was then repositioned and "postvoid" bladder counts and a static image were obtained. At the end of the study, the site of injection was imaged and counted in standardized geometry as well as an appropriate background (unpublished data).

A plasma hippurate sample was drawn 44 min after injection for the calculation of ERPF based on the theoretical volume of a three-compartmental model of OIH distribution (*9,10*). For comparison with normals, the estimated ERPF in milliliters per minute was corrected to 1.73 m^2 body surface area (*11*). All samples were counted in well scintillation counters against appropriately diluted standards with especial care taken to insure that no ^{99m}Tc counts appeared in the window chosen for ^{131}I counting.

The percent of the injected dose in the voided specimen was determined. From the net pre- and postvoid bladder counts, the residual urine volume and the percentage of injected dose retained were calculated by the formulas presented by Schlegel, et al (*12*). The total percentage of injected dose excreted was the sum of the residual and voided percentages.

The renographic curves were evaluated along with the concomitantly obtained images. Special attention to the contribution of background activity to the shapes of the curves was necessary if the split crystal technique was used. This was especially true when the excretory portion of the curve was being analyzed in patients with decreased hippurate clearance or when excessive filling of the urinary bladder spuri-

TABLE 1. ANALYSIS OF ^{131}I-ORTHOIODOHIPPURATE STUDY

	Normal	Abnormal
Uptake of OIH (0–3 min)	Prompt	Delayed
Tissue-to-background ratio (0–3 min)	Satisfactory	Low
Peak activity	3–6 min	>6 min
Visualization of collecting system	3–6 min	>6 min
Complete washout of cortical activity	27–30 min	>30 min
ERPF (ml/min/1.73 meters^2)	>250	<250 min
EI	0.8–1.2	<0.8

TABLE 2. ESTIMATED ERPF AND EI IN TRANSPLANT PATIENTS

Category	Number of studies	ERPF	EI
Normal	96	337 ± 71	0.97 ± 0.08
Acute rejection			
Impending	37	286 ± 69	0.82 ± 0.09
Actual	48	186 ± 56	0.56 ± 0.16
Chronic rejection			
Stable stage	20	157 ± 75	1.04 ± 0.08
Terminal stage	4	93 ± 45	0.51 ± 0.03
Acute tubular necrosis	8	205 ± 47	0.20 ± 0.10
Incomplete obstruction	8	317 ± 24	0.68 ± 0.10
Hypotonic ureter	12	348 ± 105	0.95 ± 0.07
Total	233		

ously contributed counts to the "kidney curve" in the transplants.

Data analysis. ERPF was calculated by the use of previously published regression equations (*9*). The percentage of the dose expected to appear in the urine was calculated from regression equations derived principally from Matthews' formulas (*13*) and based on the percentage dose in the end compartment of a three-compartment system including the end volume at any plasma clearance level.

A shortcut regression equation for ERPF values up to 250 ml/min for the prediction of the percentage OIH excreted, derived empirically, was found to be described by the polynomial:

$$\text{Percent dose expected in urine at 35 min} = 0.036 + 2.755 \times 10^{-3}\,(\text{ERPF}) - 2.967 \times 10^{-6}\,(\text{ERPF})^2.$$

For ERPF values greater than 450 ml/min, we used the expression: $0.1722 + 1.919 \times 10^{-3}\,(\text{ERPF}) - 1.509 \times 10^{-6}\,(\text{ERPF})^2$.

The EI was defined as the ratio of the actual percent dose excreted to the predicted at any given ERPF.

Data evaluation. Seven basic parameters were used to evaluate the OIH studies (Table 1). The DTPA perfusion angiograms were evaluated for uniformity of renal perfusion in the transplant, similarity of the disappearance rates of activity from the kidney, and the background area and the rate of accumulation of the radionuclide.

The static DTPA scintigrams were utilized to compare the size and shape of the kidney between studies as well as to assess the tissue-to-background ratio, which decreases with deterioration of renal function. When EI values were low, OIH scintigrams were used to locate the unexcreted OIH.

RESULTS

The estimated ERPF and EI in each category of patients as well as the number of studies performed are listed in Table 2.

The estimated mean ERPF utilizing these techniques equaled 337 ± 71 ml/min/1.73 meters² in 96 determinations in normally functioning transplants. The ERPF of the single remaining kidney in a group of 15 donors 1 week after surgery was 345 ± 68 ml/min/1.73 m². These values are not significantly different. Therefore, in the recipients, estimated ERPF values of 200–250 ml/min/1.73 m² were considered to represent the lower limits of normal, and values below 200 uniformly were regarded as abnormal, i.e., greater than two standard deviations below the group mean. The EI when evaluated by this method yielded normal values in single-kidney studies between 0.8 and 1.2 (95% confidence intervals).

Selected examples of various parts of the combined scintigraphic and quantitative hippurate excretion studies are presented in the figures. Figure 1A demonstrated a normal DTPA perfusion study in a transplant patient and is contrasted with the findings in chronic rejection (Fig. 1B), where the decrease in disappearance rates from the transplant and the background is apparent.

Impending acute rejection is illustrated in Fig. 2A where the delay in cortical clearing was sufficient to result in a decreased EI even though the ERPF and all biochemical studies were within normal limits. The progression to acute rejection occurred within 5 days with decreased uptake of OIH and prolonged transit and cortical retention times as well as delayed visualization of the collection system. Note the progressive decrease in ERPF with a disproportionate decrease in EI. Recovery following therapy is shown in Fig. 2C. (See Table 3.)

Figure 3A illustrates the value of the combined study where the patient developed incomplete subpelvic obstruction (EI decreased due to pelvic retention) with normal transplant function and a normal ERPF. Seven days later, with a small decrease in ERPF, cortical retention is observed (Fig. 3B) and the height of the kidney curve is significantly decreased. Without therapy, the patient progressed to acute rejection (Fig. 3C). (See Table 3.)

Figure 4 is a plot of the relationship between ERPF and EI in 165 studies. Five clinical categories

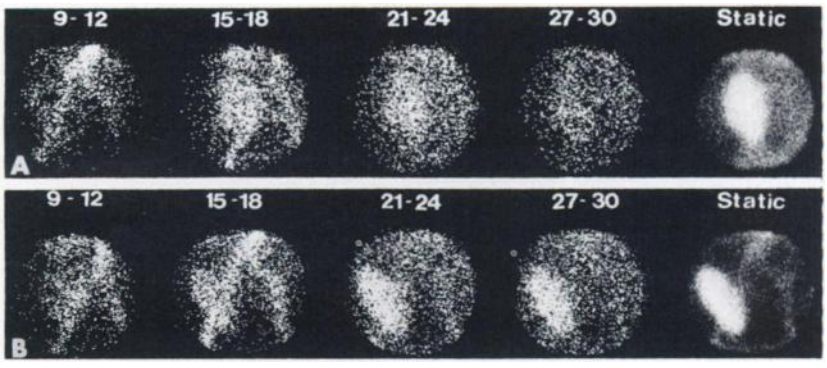

FIG. 1. Comparison of renal perfusion study using 1 mCi of ^{99m}Tc-DTPA in normally functioning transplant (A) and in chronically rejecting kidney (B). Times noted are seconds after injection; static image on far right was obtained after 5 min. In (A) note prompt visualization of kidney and similar rates of disappearance of activity from background and kidney. In (B) delayed transit of radionuclide is clearly shown as well as dissimilar disappearance rates of activity from background and kidney. Transplant size is normal in both studies.

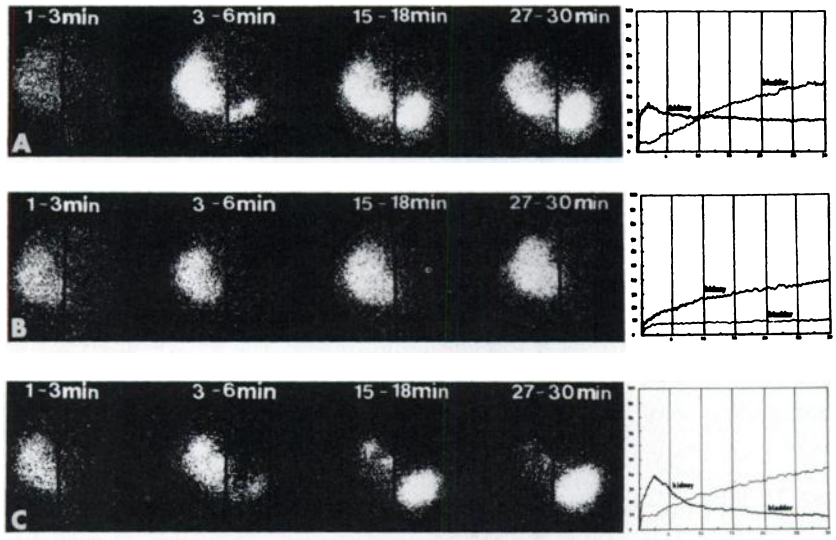

FIG. 2. Three studies during post-transplant period demonstrating value of combined study in defining (A) impending acute rejection, (B) acute rejection, and (C) return to normal transplant function. OIH clearance and excretion data are listed in Table 3. Times after injection are noted in minutes and at far right are kidney and bladder renograms. See text for further details.

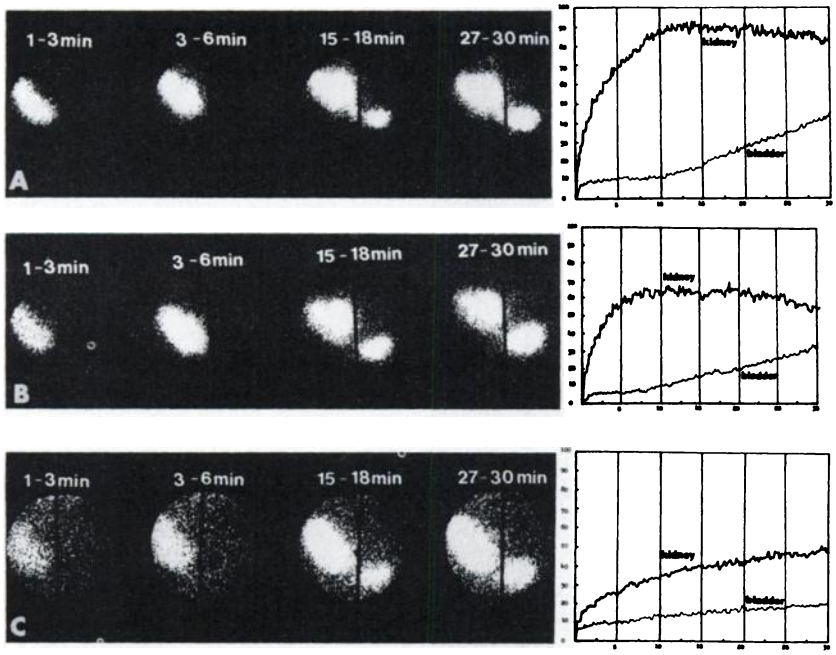

FIG. 3. Three studies during post-transplant period in patient whose data was given in Fig. 2, demonstrating (A) incomplete subpelvic obstruction and normal transplant function, (B) development of impending rejection in presence of same degree of obstruction as in (A) and (C) acute rejection. OIH clearance and excretion data are listed in Table 3. Times and renograms are as in Fig. 2. See text for further details.

are clearly separated. All clinically normally functioning transplants had estimated ERPF values greater than 250 ml/min/1.73 m^2 and EI values greater than 0.8. As illustrated, subpelvic incomplete obstruction results in a decreased EI with a normal ERPF. Impending rejection is associated with a progressive stepwise decrease in EI and a relatively maintained or slightly decreased ERPF, while actual rejection was heralded by a further decrease in both. During stable chronic rejection there was a progressive decrease in ERPF with a maintained EI, while the terminal stage was again associated with a decrease in both. Acue tubular necrosis was associated with decreased ERPF and the lowest EI values in this series (Table 2).

DISCUSSION

This study has suggested certain advantages of a combined and quantitative OIH excretion study in the evaluation of renal function and definition of several pathologic complications during the post-transplant period. The delayed cortical clearance of OIH and the associated decreased ERPF were found to antedate any biochemical or physiologic abnormality in impending acute rejection and may well represent a unique early sign of this complication. More recently therapy has been begun on patients with these findings. The decreased kidney radioactivity observed during perfusion scintigraphy in acute cell-mediated rejection probably reflected decreased

TABLE 3. OIH EXCRETION DATA FOR FIGS. 2 AND 3

	8–1 (Fig. 2A)	8–6 (Fig. 2B)	10–15 (Fig. 2C)	1–24 (Fig. 3A)	1–31 (Fig. 3B)	2–4 (Fig. 3C)
ERPF (corrected) (ml/min/1.73 m^2)	320	123	272	380	322	82
Predicted excretion (%)	61	33	55	65	61	19
Actual excretion (%)	39	5	53	28	19	9
Bladder residuum (ml)	6	5	5	22	25	10
Total excretion (%)	45	10	57	42	28	11
EI	0.74	0.3	1.03	0.65	0.46	0.55

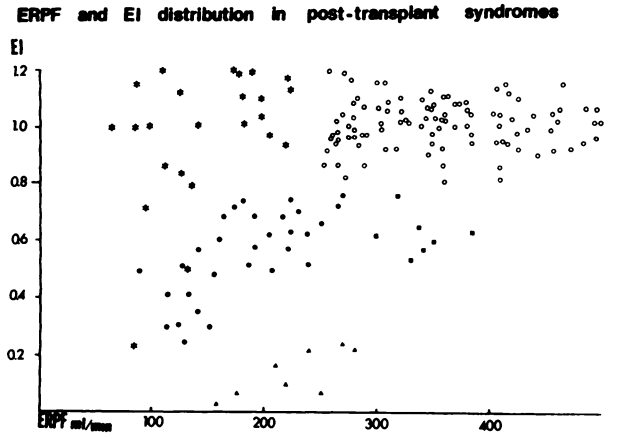

FIG. 4. Graphic representation of relationship between ERPF (abscissa) vs EI (ordinate) in normal functioning transplant patients (open circles), incomplete obstruction (solid squares), acute tubular necrosis (solid triangles), acute rejection (solid circles), and chronic rejection (asterisks). See text for additional discussion.

blood flow due to extrinsic vessel compression related to local accumulation of T-lymphocytes (*14*). This finding, occurring 7–10 days after surgery, was usually accompanied by a sequential decrease in EI and then ERPF and preceded any acute increase in plasma creatinine concentration by about 3 days in cell-mediated rejection. It should be pointed out that in our entire series approximately 3% of acute rejections were thought to represent delayed hyperacute humoral rejection mechanisms and our studies showed that in such patients the findings resembled those of chronic rejection, with a correspondingly much greater impairment in ERPF as compared to the decrease in quantitative tubular excretory capacity expressed by the EI. Indeed, during chronic rejection, the EI remains within normal limits while there is a progressive decrease in ERPF. The irreversible terminal phase is characterized by a relentless decrease in EI. Acute tubular necrosis during the early post-transplant period was always characterized by an extremely low EI without any change in kidney size in the dynamic perfusion scintigraphic study.

The combined study also successfully differentiated incomplete subpelvic obstruction and "hypotonic ureter" syndrome by noting the extent of the obstruction, which in the "hypotonic ureter" syndrome was never great enough to reduce the EI to levels below 0.8. As illustrated in the figures, the real value of the combined study is not only the accurate delineation of the several common post-transplant complications but the ability of the study to evaluate several combinations of complications which appear to require different management techniques and may not be demonstrated by simple scintigraphic studies.

It should be emphasized that the basic difference between the older continuous-infusion-type clearances advocated by Smith (*15*) and the single-injection plasma disappearance (compartment analysis) clearance advocated by Sapirstein (*16*) is crucial to the interpretation of this study.

The former are based on the quotient of urine levels to plasma levels of an indicator and would therefore be expected to be low in any clinical situation associated with a markedly prolonged renal transit time, while the latter depends only on the renal accumulation rate and not on the appearance of the indicator in the urine. Therefore, the results of the two approaches would be expected to be different in many of the cases presented here. It is likely that cases of acute tubular necrosis and acute cell-mediated rejection could not be separated by clearances calculated from continuous infusion data.

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