RADIONUCLIDES IN RENAL TRANSPLANTATION

G. Hör, H. W. Pabst, K. J. Pfeifer, P. Heidenreich, H. Langhammer, and H. G. Heinze

Nuklearmedizinische Klinik und Poliklinik der Technischen Universität and Klinik und Poliklinik für Radiologie der Universität München, Munich, Germany

In the terminal stages of renal failure, renal transplantation has become an effective means of treatment (*1,2*). Although survival rates have improved since the availability of adequate immunotherapy, present means of diagnosing the various forms of renal complications leave much to be desired.

Since 1966 180 kidney transplantations have been performed at the university clinics in Munich (*2*). Encouraged by communications of other authors (*3–9*) we have begun to use procedures involving radioisotopes, and results were compared with nephrological testing procedures (*10–15*).

Clinical diagnosis was based on the clinical course, palpation of the transplant, urine volume, serum creatinine, creatinine clearance, sodium excretion, urinary osmolarity, and biopsy.

Radiological procedures were usually confined to abdominal x-ray when kidney size was of interest. Drip infusion urography was used when extravasation of urine (urinary fistula) was suspected, and arteriography was performed to exclude arterial stenosis or thrombosis.

TABLE 1. RADIONUCLIDES IN RENAL TRANSPLANTATION

Radiopharmaceutical	Procedure	
o-^{131}I-hippuric acid	Isotope renography Effective renal plasma flow	Tubular function
^{113m}In, ^{99m}Tc-, ^{169}Yb-EDTA, -DTPA	Isotope renography Renal clearance	Glomerular function
^{203}Hg-mersalyl	Scanning	Localization
^{197}Hg-chlormerodrin	Scanning	Localization
^{131}I-fibrinogen	Scanning	Localization
^{133}Xe	^{133}Xe clearance	Renal blood flow
$^{99m}TcO_4^-$	Scintillation camera	Vascular perfusion

METHODS

Several radionuclide procedures were chosen for the evaluation of function and morphological disorders of the renal transplants. These are summarized in Table 1.

Renography. One hundred fifty-three followup studies were carried out with ^{131}I-o-hippuric acid (OIH) to estimate glomerular and tubular function. (Since OIH measures effective renal plasma flow, it is listed as tubular function in the tables and referred to as such in the test that follows.) Thirty-two patients were additionally investigated using ^{113m}In-Fe-EDTA (In) to study glomerular function alone.

^{133}Xe clearance. During preservation of an extracorporeal cadaver kidney transplant in a perfusion chamber (*16*), 200–500 μCi of radioxenon dissolved in 3–5 ml of sterile saline were injected selectively into the arterial branch of the exteriorized kidney which was mounted to the forearm of the patient.

Renal cortical blood flow (RCBF) was determined by externally monitoring the ^{133}Xe washout from the exteriorized kidney. Graphical analysis of the radioxenon disappearance curve was performed using rapid component 1, its half-time, and lambda as the partition coefficient of radioxenon between kidney blood and parenchyma, dependent on the hematocrit. RCBF was related to kidney weight.

Renal scanning. Renal scanning was performed in 62 patients using ^{203}Hg-mersalyl, ^{197}Hg-chlormerodrin, and ^{113m}In-Fe-EDTA, with a Picker Magnascanner 500.

Sequential scintigraphy. Sequential scintigraphy was carried out in another 16 patients using 250 μCi of ^{169}Yb-EDTA and a Picker Anger scintillation camera.

Renal clearance studies. Renal clearance studies were performed in 30 followup examinations. One

Received Jan. 10, 1972; original accepted May 11, 1972.

For reprints contact: G. Hör, Nuklearmed. Klin. d. TU, Ismaningerstrasse, 8 München 80, Germany.

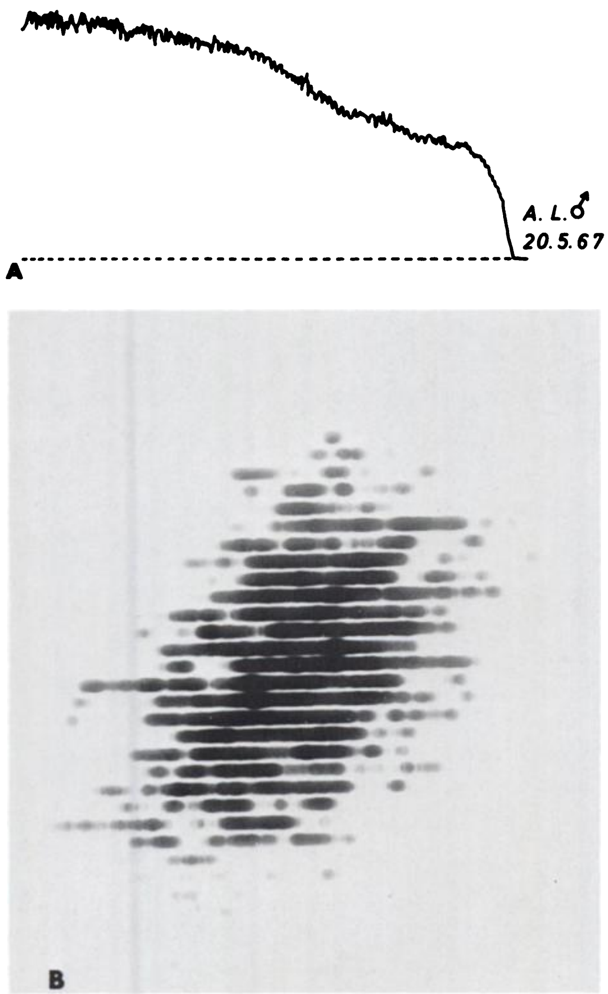

FIG. 1. (A) OIH renogram in acute rejection: OIH accumulation. (B) Photoscan (^{203}Hg-mersalyl) in anuric rejection crisis (same patient): radioactivity in periphery (cortical area) reduced, no bladder activity.

hundred fifty microcuries of OIH were given intravenously, followed by 250 μCi of ^{169}Yb-EDTA 20 min later for combined investigation of renal plasma flow (RPF), and glomerular filtration (GFR). The filtration fraction (GFR/RPF) was estimated (*17*). Renal clearance was calculated according to the whole-body principle (*18*) by externally monitoring the decline of radioactivity in the whole body, with the exception of kidney and bladder which were shielded by lead. Several plasma samples were drawn, and radioactivity (C_{plasma}) was determined in the well counter. Clearance (Cl) was calculated according to the formula of Oberhausen (*18*) separately for OIH and ^{169}Yb-EDTA:

$$Cl = \frac{-\,dm/dt}{C_{plasma}}.$$

RESULTS

In acute rejection crises the following criteria were found (Fig. 1A):

1. OIH accumulation (lack of excretory segment) or prolonged secretory maximum (T_{max}), fall in urinary osmolarity, lack of bladder activity, and marginal filling defects in the scan (Fig. 1B).

2. There is a decrease in endogenous C-CR. Correlation between parameters of radionuclide renography and the level of serum creatinine is presented in Table 2. There is a positive correlation between serum creatinine and the elimination index of the OIH and In-Fe-EDTA renograms, and a negative correlation between serum creatinine and accumulation index of renography.

3. Different behavior between tubular and glomerular function was found in acute tubular necrosis of transplanted cadaver kidneys that were subject to prolonged ischemia time before transplantation.

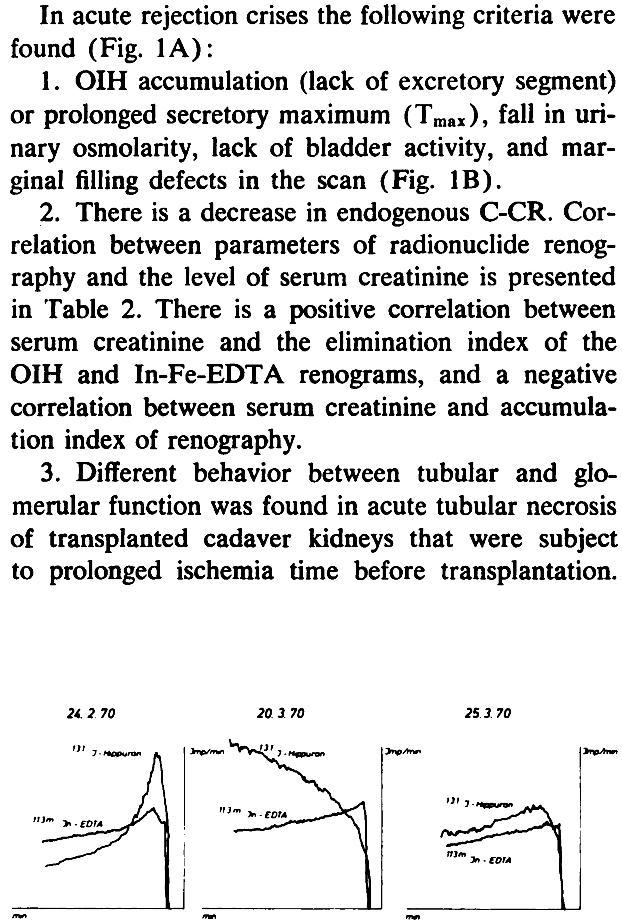

FIG. 2. Followup study with OIH- and ^{113m}In-EDTA renography in kidney transplant: rejection crisis on March 20, 1970.

TABLE 2. CORRELATION BETWEEN SERUM-CREATININE (MG%) AND ISOTOPE RENOGRAPHY (KIDNEY TRANSPLANTS)

	Tubular function			Glomerular function		
		^{131}I-o-Hippuran			^{113m}In-EDTA	
Renography	Accum. ratio	Elim. ratio	Secret. max.	Accum. ratio	Elim. ratio	Filtrat. max.
n	41	35	25	38	33	38
r	−0.662	+0.763	+0.595	−0.502	+0.530	+0.572
$b_{y/x}$	0.11	0.037	0.267	0.164	0.0678	0.950
p	<0.001	<0.001	<0.01	<0.01	<0.01	<0.01

Accumulation ratio (1.5/0.5 min-activity).
Elimination ratio (20.0/0.5 min-activity).

TABLE 3. RENOGRAPHIC FOLLOWUP STUDIES OF CADAVER KIDNEY TRANSPLANTS WITH TUBULAR NECROSIS

Total ischaemia time (min)	Normalization of renogram (days after)
239	19
203	16
159	5
155	8
115	5
109	3

As an example of differences in glomerular and tubular function in acute rejection crises see Fig. 2, second panel. Note the continuous OIH accumulation without excretion but excellent excretion of ^{113m}In-Fe-EDTA. The OIH renogram became normal on March 25, 1970.

4. In acute tubular necrosis delayed transit time of OIH seems to depend on the duration of ischemia time of the cadaver kidney before transplantation (Table 3).

5. The ^{113m}In-EDTA was found to be rapidly excreted by normally functioning transplant kidneys so that this radiopharmaceutical is more suitable for tests by the scintillation camera (Fig. 3). Arterial thrombosis or complete occlusion results in total loss of accumulation of radioactivity.

6. Rectilinear scans using ^{203}Hg-mersalyl or ^{197}Hg-chlormerodrin were characterized by filling defects in the center, in the upper, or in the lower pole of the rejected kidney as has been reported by us previously (*11*).

7. Sequential scanning after injection of ^{169}Yb-EDTA and/or OIH presented no characteristic pattern in rejection of the kidney transplant and was of no predictive value (Fig. 4).

8. Renal clearance studies, however, gave additional information concerning the functional state of the rejected transplant (Fig. 4). Simultaneous determination of the clearances of OIH and ^{169}Yb-EDTA showed disproportionate reduction of RPF compared with GFR, so that filtration in rejection crises was elevated (Fig. 5).

9. In some cases determination of the washout of ^{133}Xe in the kidney before transplantation, while preserved in a perfusion chamber, proved to be of prognostic value when RCBF has been found normal (Fig. 6).

DISCUSSION

Radionuclide renography is now an acknowledged and easily performed diagnostic tool for elucidating complications following renal transplantation.

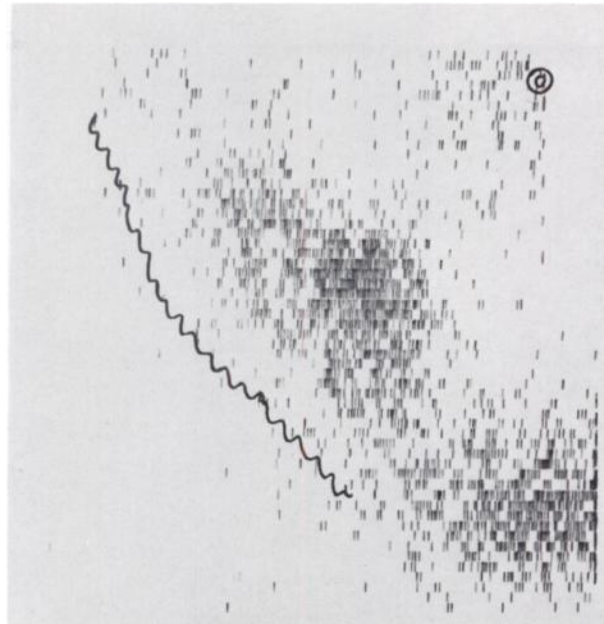

FIG. 3. Colorscan (^{113m}In-EDTA) in kidney transplant with doubled renal artery: obstruction of upper branch. Note retention of radioactivity in area of renal pelvis.

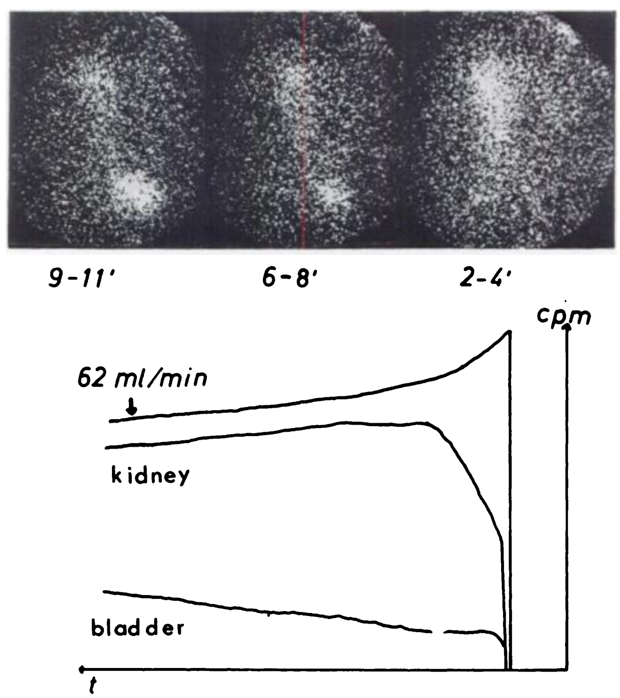

FIG. 4. Serial scintiphotography (sequential scintigraphy) and OIH-single shot clearance in acute rejection.

From our followup studies we conclude that parameters of OIH as well as of the ^{113m}In-Fe-EDTA renogram are generally in accordance with the level of serum creatinine.

Collins, et al (*3*), Sharpe, et al (*8*), and Staab, et al (*9*) have also reported on the prognostic value

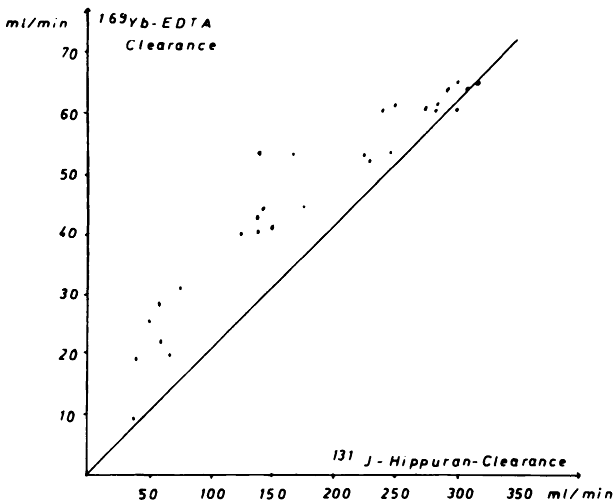

FIG. 5. Comparative glomerular and tubular clearance in transplanted kidneys.

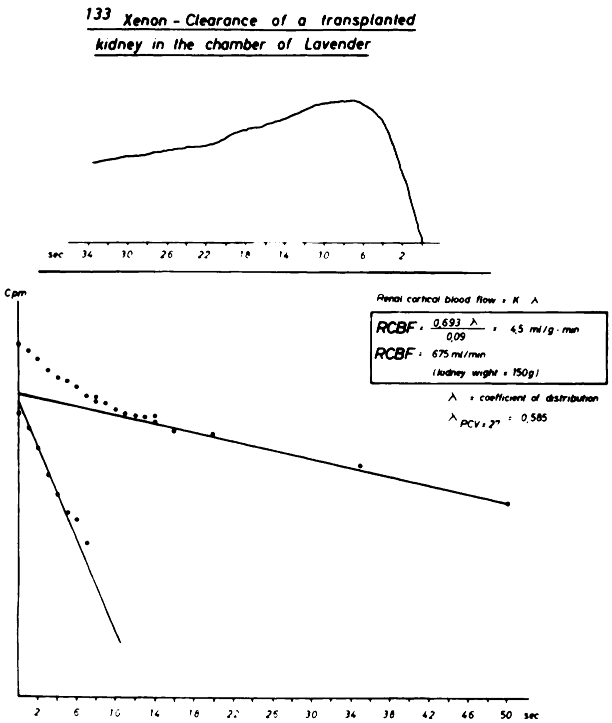

FIG. 6. RCBF study using ^{133}Xe clearance (cadaver kidney, preserved in perfusion chamber).

of radionuclide renography which may show pathological changes before clinical alterations.

The most common pathologic type is the continuous OIH accumulation with the lack of the excretory phase. This type of renogram was described as a sign of rejection by Mobley, et al (*6*). Continuous OIH accumulation, however, is not pathognomonic for rejection of kidney transplants. It may be due to rejection crisis as well as to disorders of excretion on account of a necrosis of the ureter at the level of the anastomosis.

Lubin, et al (*19*) demonstrated kidney scanning with OIH as a complementary test to renography to locate sites of abnormal accumulation. In ureteral obstruction, for instance, most of the abnormally pooled radiopharmaceutical is found in the renal pelvis, whereas in rejection it is principally cortically reduced. Furthermore renal scanning by itself may help in the differential diagnosis of oliguria. In necrotic renal allografts obtained from cadaver donors no uptake of ^{203}Hg-chlormerodrin is observed (*4*). In total obstruction of the renal artery due to complete stenosis or to thrombosis we regularly observed a nephrectomy-type of renogram. Immediately after intravenous injection of OIH, radioactivity disappears over the kidney transplant similar to the blood disappearance curve which is externally registered over the heart. Acute tubular necrosis may be associated with accumulation as well as with nephrectomy type. In our hands, simultaneous performance of radionuclide renography using OIH and ^{113m}In-Fe-EDTA was valuable in differentiating between the onset of glomerular and tubular function in cadaver kidneys. Similar observations were reported by zum Winkel, et al (*20,21*) using sequential scintigraphy with the Anger camera. This technique is superior to conventional scanning, especially when used in conjunction with a computer, because it supplies both functional and morphological data (*20–23*).

The following criteria were described in rejection crises (*20*): (A) reduced initial uptake of OIH, (B) delay in intrarenal transport of OIH, and (C) decreased renal excretion.

There are also differences in the radioactivity pattern associated with acute tubular necrosis (reduced accumulation) and renal artery thrombosis (lack of accumulation).

Clearance procedures represent another step forward in expanding diagnostic possibilities after renal transplantation (*7,17,24–26,31*). The superiority of these methods over scanning procedures is evident because renal functional impairment may be quantitated. Comparative studies including the estimation of GFR and RPF, as carried out by us, demonstrated that in rejection crisis RPF is more severely reduced than glomerular function. Similar observations were published by Rosen, et al (*27*).

Renal ^{133}Xe clearance supplies information concerning cortical blood flow of the kidney transplant (*14,15,27–29*). The practicability of this method, however, is very limited. Radioxenon has to be injected selectively into each renal artery, so this clearance technique is applicable only to the Seldinger technique or during surgery (intraoperative xenon clearance) (*29*), in cases of inevitable arteriography (in arterial stenosis, thrombosis), or, in accordance with our practice, in extracorporeal kidney transplants preserved in a perfusion chamber (*14,15*). This procedure offers the possibility of preserving cadaver kidneys prior to transplantation until function and histocompatibility are tested (*16*). RCBF may be determined using the most rapid component (Fig. 6), and progressive redistribution of blood flow is seen in rejection because of hypoperfusion of the renal cortex as has been shown by autoradiography (*27*). This reduction in RCBF is considered to be caused by immunological mechanisms and may play a role in the ensuing renal failure.

Single injection clearance of OIH has been promoted by Rösler (*7*), Blaufox, et al (*24*), and Gott, et al (*25*). The volume of distribution (V) of the injected OIH, calculated from the injected dose divided by the zero intercept of blood disappearance curve times the slope ($k = 0.693/\text{half-time}$) enables one to evaluate the clearance (Cl) of the kidney transplant: $Cl = V \times K$ (one-compartment concept). Renal clearances are reduced early in rejection crises, where, on account of the oliguria, urinary sodium excretion and urinary osmolarity are unobtainable. According to Rösler (*7*) simultaneous application of radionuclide renography with OIH and single-injection clearance gives quantitative information concerning the total clearance of the kidney transplant.

Simplified clearance techniques based only on the determinations of half-time of the blood disappearance curve (*30*) or on the one-compartment concept did not correlate with standard clearance procedures (*31*). At the present time we believe one cannot decide whether the single-injection clearance calculated according to one-compartment, two-compartment, or multicompartment models is best suited for replacing conventional clearance procedures (*14*). A really new idea obviating the compartment idea was developed by Oberhausen (*18*) in measuring the total-body clearance of renal clearance substances. Up to the present time, however, experiences with this technique in kidney transplants are limited.

Reviewing our own results and those reported in the literature it seems justifiable to use radioisotopic procedures to determine function and morphology of kidney transplants. Exact and comparable interpretation of the results obtained so far will depend however on standardizing examination procedures to be performed by nuclear medicine personnel.

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