Deconvolution Analysis of Renal Blood Flow: Evaluation of Postrenal Transplant Complications

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Medical complications after renal transplantation cause problems in treatment decision making. To differentiate acute tubular necrosis from acute rejection when it occurs in the early post-transplant period is difficult. Renal scintigraphy offers a noninvasive means for renal blood flow (RBF) and renal function assessment. **Methods:** This retrospective study of RBF and renal function evaluation after kidney transplantation is an attempt to calculate the "renal vascular transit time" from the ^{99m}Tc-diethylenetriaminepentaacetic acid renal vascular flow with a deconvolution technique. The results of 102 studies on 38 graft recipients were evaluated. Of these, 19 were diagnosed as acute rejection, 12 as acute tubular necrosis, 4 as chronic rejection, 1 as vesicoureteric reflux, 1 as recurrent immunoglobulin A nephropathy, 1 as iliac vein thrombosis, 1 as cyclosporine nephrotoxicity and 63 as normal. All diagnoses were established by clinical and/or pathologic criteria. **Results:** With renal vascular transit times more than 12.8 sec, the sensitivity and specificity for the detection of acute rejection was 95% and 94%, respectively. The sensitivity and specificity for the differential diagnosis of acute rejection against acute tubular necrosis was 95% and 92%, respectively. **Conclusion:** The use of renal vascular transit time in addition to ^{131}I-labeled hippuran renogram provides a promising diagnostic parameter to differentiate between acute rejection and acute tubular necrosis.

Key Words: radionuclide study; renal transplantation; renal vascular transit time; deconvolution

J Nucl Med 1994; 35;1792–1796

Many quantitative renal radionuclide scintigraphic methods have been used to evaluate renal allograft function. Some of these are the perfusion index (*1*), kidney-to-aorta perfusion ratio (*2*), cortex perfusion index (*3*) and washout parameter (*4,5*). However, these methods have the practical disadvantage of requiring a good intravenous bolus injection of tracer. Another problem is that these parameters are count based and they can be influenced by the size and site of the region of interest (ROI). These problems can be solved theoretically by the deconvolution method (*6,7*). The aim of this study was to investigate the feasibility of applying the deconvolution operation to the renal blood flow (RBF) time-activity curve to obtain the impulse response function of the renal vasculature from which the renal vascular transit time (RVTT) can be calculated. The RVTT is then used in conjunction with the hippuran renogram to evaluate postrenal transplant complications.

MATERIALS AND METHODS

Patients

Thirty-eight patients who underwent renal transplantation between March 1982 and January 1993 at Chulalongkorn University Hospital and whose clinical data were available were studied retrospectively. A radionuclide renographic study with ^{99m}Tc-labeled diethylaminetriaminepentaacetic acid (DTPA) and ^{131}I-labeled hippuran and ultrasonography of the transplanted kidney were routinely performed in the first 48 hr and at 1 wk, 2 wk and 1 mo after surgery. They were repeated whenever there was a clinical indication.

Imaging Technique

The gamma camera was positioned anteriorly over the renal allograft in the pelvic cavity, which included the distal part of the abdominal aorta. The study was performed after intravenous injection of 10 mCi (370 MBq) of ^{99m}Tc-DTPA through an anticubital vein. The images were obtained with a large-field-of-view gamma camera (GE 400 ac) that used an all-purpose, low-energy parallel-hole collimator. Two-phase digital dynamic images were obtained on the magnetic disk of a computer (Starcam) at the rate of 1 frame/sec for 40 frames, followed by 1 frame/20 sec for the next 80 frames on a 128 × 128 matrix word mode. After the ^{99m}Tc-DTPA study was finished, ^{131}I-hippuran imaging was performed after intravenous injection of a dose of 300 μCi (11.1 MBq) through the same intravenous line. A medium-energy, parallel-hole collimator was used. A one-phase, 1-frame/min digital image was obtained for 30 frames on a 64 × 64 matrix word mode.

Quantitation

The time-activity curve of ^{131}I-hippuran was generated with the irregular ROI of the whole kidney. The time-to-peak activity was

Received Nov. 18, 1993; revision accepted May 27, 1994.

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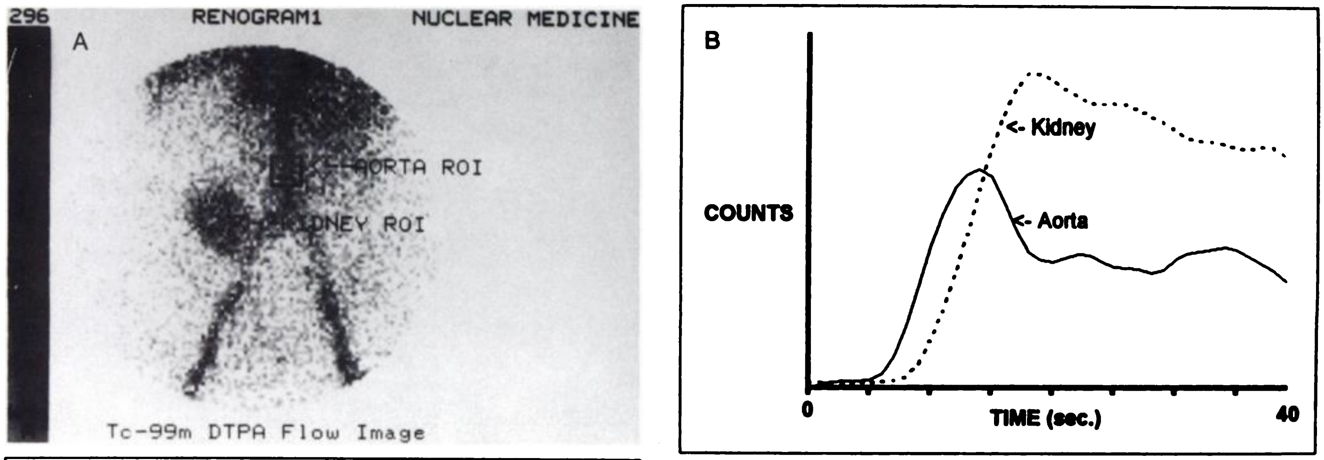

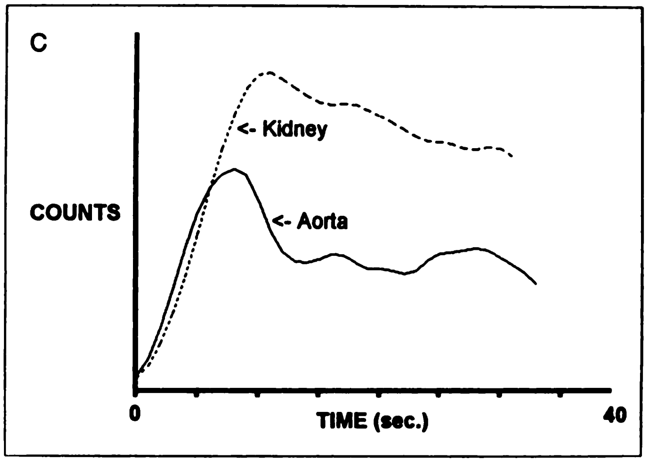

FIGURE 1. (A) DTPA flow image with renal and aortic ROI. (B) RBF and aortic blood flow time-activity curves of the first 40 sec. (C) The curves after time points with maximum acceleration of count rate were placed at time zero.

then determined by computer. To analyze ^{99m}Tc-DTPA data, only the first 40 frames (1 sec) were used. When the ROI was drawn, all frames were summed and then one 10 × 10-pixel square regular ROI was placed over the distal aorta just proximal to the iliac bifurcation. Another ROI of the same size was placed over the renal graft (Fig. 1A). Time-activity curves of the first 40 sec were drawn (Fig. 1B). To avoid intra- and interoperator variation of the distance between aortic and renal ROIs, which could affect the results of the deconvolution, both aortic blood flow and RBF curves were shifted so that the time points with maximum acceleration of the count rate, which were equivalent to the maximum of the second differentiated function of the flow curves, were placed at time zero (Fig. 1C). The deconvolution operation, which used the aortic blood flow time-activity curve as an input function, was performed based on the appended curve technique developed by Juni et al. (*8*). This is a modification of the Fourier transform method. The resulting impulse response curve was then smoothed by the Butterworth filter. Because the degree of smoothing can influence the appearance of the curve (and hence the transit time), varying power factors of 5, 10, 15 and 20 and frequency cutoffs of 0.125, 0.167 and 0.250 Hz were used in curve smoothing to determine the best parameter for the Butterworth filter. Then the plateau was applied to the initial part of the impulse-response curve, and the transit time was calculated by dividing the area under the impulse-response curve from time zero to the zero crossing point by the plateau value (Fig. 2) as in Equation 1 (*6*).

$$\text{Transit time} = \frac{H(t)dt}{H(t = 0)}, \qquad \text{Eq. 1}$$

where H(t)dt = area under the impulse-response curve, H(t = 0) = plateau value.

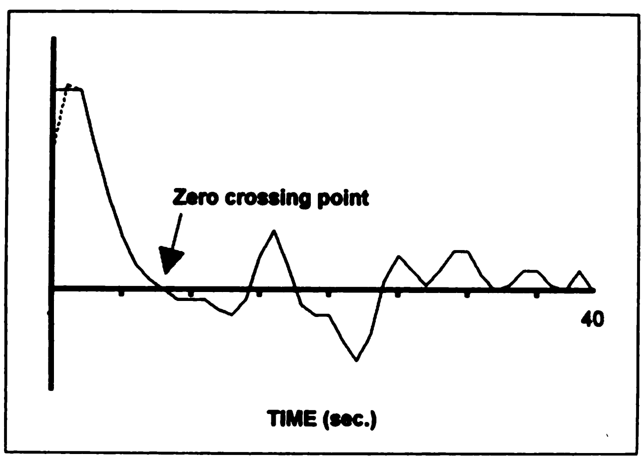

FIGURE 2. Impulse-response curve. Dashed and solid lines represent original curve and curve in which the initial part was modified into a plateau, respectively.

Diagnostic Criteria

The following criteria were used to classify the renal graft.

A. Normal functioning graft
 1. Good urine production of at least 2 ml/min.
 2. Serum creatinine level not more than 2.0 mg/dl.
 3. No signs and symptoms of rejection on the day of the study and within the following week.
 4. Normal appearance of hippuran renogram (*9*) and/or a normal ultrasonographic study.

B. Acute tubular necrosis (ATN)
 1. Delayed and prolonged peak of the second phase of the hippuran renogram.
 2. No signs and symptoms of rejection on the day of the study and within the following week.
 3. Clinical and hippuran renographic improvement after supportive therapy only.

C. Acute rejection (AR)
 1. There were signs and symptoms of AR, such as graft tenderness, pyrexia, rising levels of blood urea nitrogen or creatinine or decrease in the creatinine clearance.
 2. Evidence of rejection confirmed by biopsy (*10*) and/or clinical improvement after specific treatment for acute graft rejection.

Specific treatment for AR consisted of intravenous administration of 1 g of methylprednisolone for 3 days, followed by 0.5 g for another 2 days. If renal function did not improve, 5 mg of OKT3 monoclonal antilymphocyte antibody was intravenously administered for 10 days.

In cases of chronic rejection and recurrent immunoglobulin (Ig)A nephropathy, the diagnosis was made by graft biopsy. Vesicoureteric reflux with hydroureter and hydronephrosis and iliac vein thrombosis were diagnosed by voiding cystourethrography and venography respectively. In the case of cyclosporine (CyA) nephrotoxicity, the CyA level was 620 ng/ml, and renal function was dramatically improved, with increased creatinine clearance from 11.6 ml/min to 60.1 ml/min after a decrease in the CyA dose.

Exclusion Criteria

Patients were excluded from the study if their medical records were incomplete which prevented proper classification. Also, if the data acquisition was so poor that the time point with maximum acceleration of any flow curve count rate was earlier than the fourth time point, that patient was also excluded.

RESULTS

These 38 studied cases consisted of 25 men and 13 women with a mean age of 36.6 ± 9.7 yr (mean ± 1 s.d.). The average duration of postoperative follow-up was 2 yr (range = 1 mo to 8 yr). Thirteen patients received a renal graft from a living related donor and the rest from cadavers. A total of 113 studies were performed. The findings of 11 studies were excluded because of incomplete clinical data in three studies and poor data acquisition in eight studies. Of the remaining 102 studies, there were 63 normal functioning grafts, 19 ARs, 12 ATNs, 4 chronic rejections and 4 miscellaneous diagnoses. In AR, the findings of 10 studies were confirmed by biopsies, and 9 studies were diagnosed on the basis of clinical improvement with specific treatment for AR.

The group of miscellaneous diagnoses included vesicoureteric reflux with hydroureter and hydronephrosis (n = 1), recurrent IgA nephropathy (n = 1), left iliac vein thrombosis (n = 1) and CyA nephrotoxicity (n = 1).

The term RVTT was used for the transit time that was calculated from the deconvolution technique. Tables 1, 2 and 3 show p values of unpaired Student's t-tests of the mean RVTT of normal functioning graft versus AR, normal functioning graft versus ATN and AR versus ATN, respectively. It is clear that almost any degree of smoothing of the impulse-response curves gives a significantly different RVTT between AR to that of a normal functioning graft and that of ATN with the best p values of 1.92×10^{-8} when the power of 5 and frequency cutoff of 0.167 Hz was used. However, there is no significant difference between the RVTT of a normal study and that in ATN ($p > 0.05$). Because of the small number of chronic rejections and miscellaneous diagnoses, the mean RVTT could not be compared. The means and s.d. of RVTT of normal functioning grafts, AR, ATN, chronic rejection and the miscel-

TABLE 1
Unpaired t-Test p Values of Mean Renal Vascular Transit Time in Normal Graft Versus Acute Rejection When Varying Degrees of Smoothing with Butterworth Filter Were Used

	p Values at cutoff frequency (Hz)		
Power	0.250	0.167	0.125
5	0.00487	1.92×10^{-8}	0.00001
10	0.00888	0.00047	0.00168
15	0.00001	0.00007	0.01737
20	0.00011	0.00021	0.02831

TABLE 2
Unpaired t-Test p Values of Mean Renal Vascular Transit Time in Normal Graft Versus Acute Tubular Necrosis When Varying Degrees of Smoothing with Butterworth Filter Were Used

	p Values at cutoff frequency (Hz)		
Power	0.250	0.167	0.125
5	0.49114	0.14518	0.05684
10	0.39828	0.69812	0.06924
15	0.39657	0.45927	0.50219
20	0.50499	0.97837	0.73110

TABLE 3
Unpaired t-Test p Values of Mean Renal Vascular Transit Time of Acute Tubular Necrosis Versus Acute Rejection When Varying Degrees of Smoothing with Butterworth Filter Were Used

	p Values at cutoff frequency (Hz)		
Power	0.250	0.167	0.125
5	0.33146	2.80×10^{-11}	4.71×10^{-7}
10	0.00649	0.00061	0.00016
15	0.00005	0.00007	0.00598
20	0.00036	0.00165	0.01582

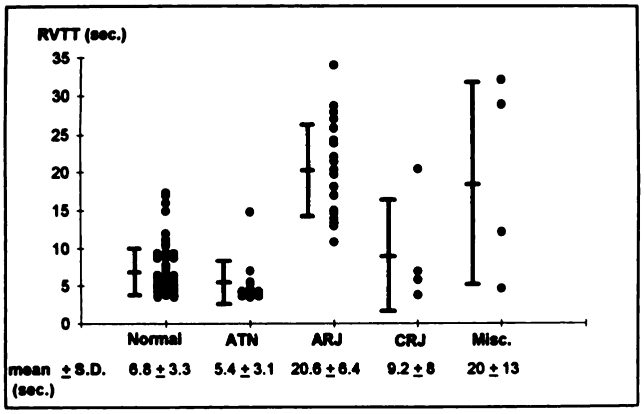

FIGURE 3. Individual transit time in five classified groups. Vertical bar indicates mean ± 1 s.d.

laneous group are shown in Figure 3. The RVTT of each case of vesicoureteric reflux with hydroureter and hydronephrosis, recurrent IgA nephropathy, left iliac vein thrombosis and CyA nephrotoxicity were 28.9, 12.2, 4.6 and 32.1 sec, respectively.

With the receiver-operator characteristic (ROC) curve as a guide, the optimal RVTT cutoff value of 12.8 sec can diagnose AR with 95% sensitivity and 94% specificity. The optimal RVTT of 12.8 sec as a cutoff value can also differentiate AR from ATN with 95% sensitivity and 92% specificity. Figure 4 demonstrates serial RVTT of a patient in whom an AR episode developed during the follow-up period.

DISCUSSION

In AR, the primary target of the host's immune attack to the renal allograft is vascular endothelium, which causes damage to the microcirculation (*11,12*) and results in vessel narrowing or occlusion of the vascular lumen (*13*). In contrast to AR, the major pathologic changes in ATN are caused by ischemic damage to the transplanted kidney, which usually arises from complete interruption of the RBF during harvesting and implanting of the transplanted kidney (*14*). The RBF in ATN is usually 25%–50% of normal and rarely shows marked impairment (*15*).

The major pathophysiologic difference between AR and ATN is in the RBF, which is impaired by AR but relatively preserved in ATN. Therefore, it is the RBF that has been studied in most reports. This consisted in the rate of vascular inflow (*1–3*) or outflow (*4*). However, all of these methods require a good bolus injection of radioisotope to obtain reliable and accurate results. To avoid this problem, deconvolution analysis of the data was introduced and has been widely applied to analyze renogram data to obtain the impulse response function of the renal parenchyma so that the renal parenchymal transit time can be calculated (*7,16,17*).

The deconvolution technique has also been used to analyze the blood transit time in several organs, such as the heart (*18*), lung (*19*) and arteries of the leg (*20*), and in the quantitation of left-to-right cardiac shunts (*21*). For the kidney, Coulam et al. (*18*) used this technique to obtain blood transit times or transfer function. Burrows et al. (*22*) reported the successful use of the technique in analyzing the RBF in animals. In the current study, the authors did not try to calculate RBF as Burrows et al. (*22*) did, but simply used the deconvolution technique to calculate the transit time of the blood flow through renal vasculature. In 1981, Rutland (*23*) claimed that the deconvolution method was susceptible to errors and suggested a new method to calculate the mean transit time without deconvolution. However, his method required several steps for the calculation. The authors can do deconvolution in only one step, which requires no more than 2 sec. With the filtering technique to eliminate the effect of data fluctuation, the authors have shown successful results that were comparable with Rutland's method in the evaluation of renal transplantation (*24*).

This study demonstrates that the RVTT in an acute episode of renal allograft rejection is significantly longer than that in the normal functioning graft. This can be explained by the pathologic finding of vessel narrowing (*15*). The increased vascular resistance causes a decreased blood flow velocity through the renal vascular network. In contrast, in ATN, where the vascular structure is preserved, the RVTT is similar to that of a normal functioning graft. However, in chronic rejection and other miscellaneous diagnoses, RVTTs vary widely. This may be due to varying degrees of pathologic changes. The RVTT gives high sensitivity and specificity in the differential diagnosis of AR from normal kidneys and ATN. The RVTT was obviously prolonged when there was an episode of rejection and declined when renal function was improved. It is useful in the monitoring of renal graft function.

CONCLUSION

The deconvolution technique can be applied to RBF in a renal scintigraphic study by using the aortic blood flow

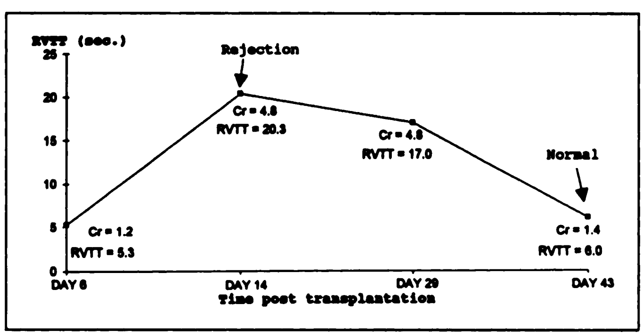

FIGURE 4. A 37-yr-old female patient who received a renal graft from a living related donor. The graft function was normal after transplantation. On the second week post-transplantation, her temperature began to rise with graft tenderness. Biopsy revealed AR. The RVTT was 20.3 sec. After treatment, her symptoms gradually improved. The follow-up RVTT was 17.0 sec on Day 29 and became normal on Day 43.

time-activity curve as an input function. This method eliminates the need for a large bolus injection. The data processing is simple. This technique, together with a hippuran renogram study, has a good sensitivity and specificity in the differential diagnosis between AR and ATN.

ACKNOWLEDGMENTS

The authors thank all personnel of the Nuclear Medicine Division and the Department of Medicine for their assistance and Prof. Henry Wilde, MD, for his excellent help in reviewing the manuscript.

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