

# Quantitation of Renal Parenchymal Retention of Technetium-99m-MAG3 in Renal Transplants

Yi Li, Charles D. Russell, Jeanne Palmer-Lawrence and Eva V. Dubovsky

*Department of Nuclear Medicine, First Hospital, Sun Yet-Sen University of Medical Sciences, Guangzhou, Guangdong, China; Division of Nuclear Medicine, University of Alabama Hospital, University of Alabama at Birmingham Medical Center and Nuclear Medicine Service, Veterans Affairs Medical Center-Birmingham; and Department of Pathology, University of Alabama Hospital, Birmingham, Alabama*

When imaging renal transplants with tubular agents, such as mercaptoacetyltriglycine, marked parenchymal retention is a hallmark of acute rejection (AR) or acute tubular necrosis (ATN). (AR can be distinguished from ATN by the time course on serial studies.) The quantitative relationship of retention to uptake can be measured by dividing the background-corrected renal activity at 20 min by that at 3 min. **Methods:** The diagnostic value of this ratio ( $R_{20/3}$ ) was tested in a series of 555 renograms. Because patients with mild disease have minimal abnormalities, the patients were ranked by their estimated severity of disease (1–4 for abnormal and 0 for normal). **Results:**  $R_{20/3}$  was found to correlate strongly with severity of ATN (Spearman's  $\rho = 0.879$ ,  $p < 0.001$ ,  $n = 168$ ) and also with severity of AR ( $\rho = 0.888$ ,  $p < 0.001$ ,  $n = 267$ ). There were two (3%) false-positive results in 64 normal patients. **Conclusion:** If 0.8 is taken as the upper limit of normal for  $R_{20/3}$ , then among patients with disease severity 3 or 4, there were no false-negative findings in 104 patients with ATN or in 203 patients with AR.  $R_{20/3}$ , despite its simplicity, is an effective diagnostic parameter.

**Key Words:** renal parenchymal retention; renal transplant; mercaptoacetyltriglycine.

**J Nucl Med 1994; 35:846–850**

**R**enal parenchymal retention of mercaptoacetyltriglycine (MAG3) and orthodohippurate (OIH) is a well-recognized hallmark of acute rejection (AR) or acute tubular necrosis (ATN). A quantitative measure of such retention is useful for monitoring the patient's course on sequential examinations. At the authors' clinic, one such measure, the excretory index (EI), has been in routine use for nearly 20 yr (1–3). The EI is used to detect the onset of rejection, to monitor the response to therapy and to distinguish ATN (which improves after the baseline post-transplant study) from AR (which shows deterioration on successive studies). However, the measurement of EI is cumbersome, involving the collection and counting of urine specimens

and a correction for postvoiding residual volume using pre- and postvoiding bladder images.

The purpose of the present study is to evaluate a simpler quantitative measure of parenchymal retention. A previously reported pilot study (4) indicated that the ratio of background-corrected renal counts at 20 min to that at 3 min conveyed diagnostic information similar to the EI. Here a detailed evaluation is presented in a larger series of patients.

## METHODS

Five hundred fifty-five  $^{99m}\text{Tc}$ -MAG3 renal transplant studies from the clinic were reviewed. These were approximately sequential, although in the severe-disease categories, the sample size was augmented by the selection of additional cases that were out of sequence. EI values (obtained from the routine report) were calculated, as described previously (3). Using a whole kidney region of interest (ROI), the ratio of the background-subtracted 1-min count at 19 to 20 min after injection to that at 2 to 3 min ( $R_{20/3}$ ) was calculated from time-activity data recorded at the time of the initial study. A circumferential ROI around each kidney was used for background correction. The site of injection was imaged in each case to exclude significant infiltration of the injected dose.

The patients were assigned a clinical classification on the basis of the chart review, assigning a diagnosis from a combination of previous history, subsequent course, laboratory measurements and, when available, biopsy or nephrectomy findings. The diagnostic classes used were normal (72 cases), ATN (145), AR (265), chronic rejection (33), cyclosporine-induced toxicity (12) and other (28 cases). To deal with ambiguities in classification, the reliability of the diagnosis in each case was assigned a grade from 0 to 4. To deal with variations in the severity of disease, the severity was also assigned a grade from 0 to 4 in each case. The severity grade was assigned as follows: grade 0, no evidence of disease or normal post-transplant course with dramatic fall in creatinine; grade 1, ambiguous clinical course with mildly elevated creatinine level (2.1–2.4 mg/dl or increase  $< 0.5$  mg/dl from baseline); grade 2, typical but mild clinical course, mild severity on biopsy, creatinine typically 2.5 to 3.0 mg/dl, increase  $> 0.5$  mg/dl from baseline of 2.0 or lower; grade 3, typical clinical course of moderate severity, biopsy findings of mild or moderate severity, creatinine typically 3.0 to 5.0 mg/dl with slow recovery or no recovery; and grade 4, typical and severe clinical course, moderate or severe disease on biopsy, creatinine typically  $> 5$  mg/dl with poor or no recovery. Patients not exactly fitting one of these

Received July 13, 1993; revision accepted Jan. 20, 1994.

For correspondence or reprints contact: Charles D. Russell, MD, PhD, Division of Nuclear Medicine, University of Alabama Hospital, 619-19th Street South, Birmingham, AL 35233-6835.

categories were assigned to the nearest category, according to clinical judgment. Factors that could interfere with the accuracy of the measurement (pelvic retention, overlap of kidney by bladder or infiltration seen on the injection site image) were also graded on a scale from 0 to 4.

Cases in which the diagnosis was unreliable (reliability grade < 3) were excluded when correlating  $R_{20/3}$  or EI with the diagnosis but were included when correlating  $R_{20/3}$  with EI.

Functional images of  $R_{20/3}$  were obtained by dividing the 1-min image at 19 to 20 min after injection by the 1-min image at 2 to 3 min after injection, correcting for background and, if necessary, manually translating the images to compensate for the patient's motion. A semilunar ROI lateral to the kidney was chosen as the background for the functional images (but not for the numeric data, which used a circumferential ROI). A manual ROI was drawn surrounding the kidney, and the region external to this ROI was masked off to eliminate distracting background noise. The numeric values of  $R_{20/3}$  were displayed on a color code that identified the ranges: < 0.1, 0.1–0.4, 0.4–0.8, 0.8–1.2, 1.2–1.6, 1.6–2.0, 2.0–2.4, 2.4–2.8 and > 2.8.

To estimate parenchymal  $R_{20/3}$  from the functional image, the predominant color was selected from parenchyma that was overlaid neither by bladder or collecting system nor was so peripheral as to be unduly sensitive to patient motion.

## RESULTS

For various technical reasons, the EI or the  $R_{20/3}$  could not be measured in every case. Of the 555 cases, the EI could not be measured in 307, and the  $R_{20/3}$  could not be measured in 135. The technical problems in the case of EI were failure to void (51 cases), indwelling catheter (43), large postvoiding residual volume (145), significant native kidney or prior renal graft function (none in this series), overlap of bladder by kidney on images (21), pelvic retention greater than grade 2 (26), dose infiltration (22), administration of furosemide during renography (none in this series) or other (9). In the case of the  $R_{20/3}$ , the problems were overlap of bladder by kidney on images (21 cases), pelvic retention greater than grade 1 (104), dose infiltration (22), administration of furosemide during renography (none in this series) or other (5). (Dose infiltration, administration of furosemide, overlap between kidney and bladder and marked pelvic retention invalidated both measures. However, because  $R_{20/3}$  was more sensitive than EI to pelvic retention, retention grades 0 to 1 were accepted for  $R_{20/3}$  and grades 0 to 2 for EI). To sum up, measurement of EI was technically unsuccessful in 307 of 555 cases;  $R_{20/3}$  failed in only 135 of 555.

After these exclusions on technical grounds, there remained 207 cases in which both  $R_{20/3}$  and EI could be measured. The correlation between these two measures of parenchymal retention is shown in Figure 1. Despite the evident correlation, there is a great deal of scatter.

For the two largest disease categories, AR and ATN, both  $R_{20/3}$  and EI were correlated with the severity of disease (graded 0–4). For this purpose, cases with a reliability of diagnosis below grade 3 were excluded (31 of 555).

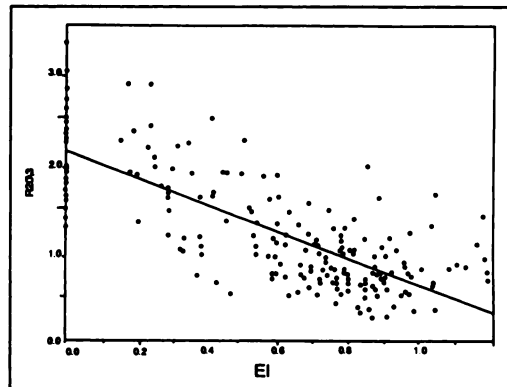


FIGURE 1. Correlation between  $R_{20/3}$  and EI. The equation of the best straight line is  $y = 2.09 - 1.49x$ , but the true relation may be curvilinear. The correlation coefficient is 0.76.

After this exclusion and exclusions for the technical reasons described earlier, there remained 203 cases of AR with technically valid  $R_{20/3}$ , 129 cases of AR with valid EI, 104 cases of ATN with valid  $R_{20/3}$ , 44 cases of ATN with valid EI, 64 normals with valid  $R_{20/3}$  and 34 normals with valid EI.

For these groups, the Spearman rank correlation coefficients (with normals included) are shown in Table 1. Values near +1 and -1 indicate a strong positive or inverse correlation, and values near zero indicate a poor correlation. The correlations are all highly significant ( $p < 0.001$ ). Observe that the correlation was stronger for  $R_{20/3}$  than for EI. Significance tests for Spearman's rank correlation coefficient are not readily available, but because  $R_{20/3}$  is technically simpler than EI, it should suffice to show that it is at least as good a diagnostic test as EI; it need not be significantly better. Table 1 shows that  $R_{20/3}$  is at least as good as EI.

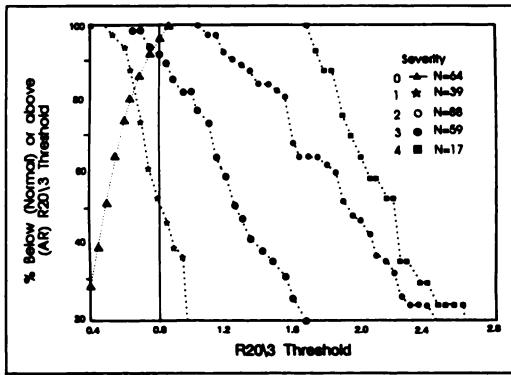
For the 12 patients who were believed clinically to have cyclosporine-induced toxicity, the  $R_{20/3}$  was minimally elevated (mean 0.84, range 0.59–1.38), and the effective renal plasma flow (ERPF) was minimally depressed (mean

TABLE 1  
Correlation of Four Diagnostic Criteria with Clinically Assessed Severity of Disease for Acute Rejection and Acute Tubular Necrosis

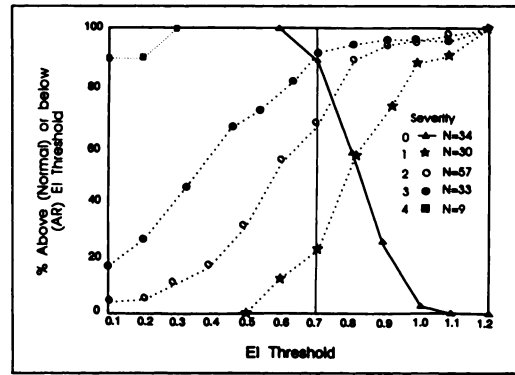
	AR		ATN	
	Spearman's $\rho$	n	Spearman's $\rho$	n
$R_{20/3}$	0.888	267	0.879	168
EI	-0.654	163	-0.696	78
ERPF	-0.578	327	-0.698	215
Functional image*	0.865	169	0.843	104

\*Visual classification method.

$R_{20/3}$  = ratio of background corrected renal activity at 20 min divided by that at 3 min; EI = excretory index; ERPF = effective renal plasma flow.



**FIGURE 2.** Correlation between  $R_{20/3}$  and severity of AR. Percentage of cases falling below (in case of normals) or above (in case of abnormals) specified threshold values of  $R_{20/3}$  for four different grades of disease severity. The recommended threshold of 0.8 is marked on the plot.



**FIGURE 4.** Correlation between EI and severity of AR. Percentage of cases falling above (in case of normals) or below (in case of abnormals) specified threshold values of EI for four different grades of disease severity. The recommended threshold of 0.7 is marked on the plot.

172 ml/min, range 100–235). The EI was normal (mean 0.91, range 0.81–1.04).

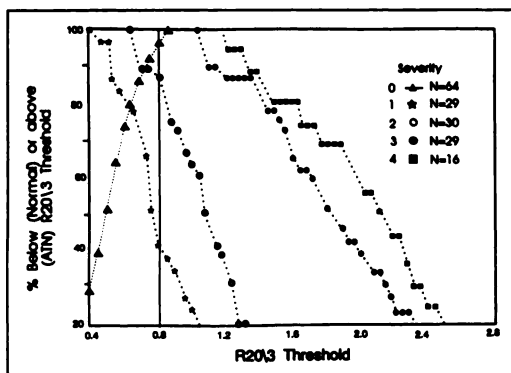
Functional imaging was performed on a subgroup that included patients for whom a meaningful  $R_{20/3}$  could not be measured directly (most commonly because of moderate pelvic retention) and 15 normals, 17 patients with ATN and 36 patients with AR. These results are also shown in Table 1. Observe that the visual classification from functional images yielded results similar to numeric measurement.

To illustrate these findings better, the cumulative frequency distributions for  $R_{20/3}$  and EI are shown in Figures 2 to 5. A threshold for separating positive from negative results can be chosen from these curves, according to the desired trade-off between sensitivity and specificity. At an intersection of curves, the probability of a false-negative finding equals the probability of a false-positive one. The values chosen for subsequent analysis in this article and that the authors recommend for general use are marked on the plots. These are 0.8 for  $R_{20/3}$  and 0.7 for EI. The mean  $\pm$  s.d. of  $R_{20/3}$  for the 64 normals was  $0.50 \pm 0.16$ . For the

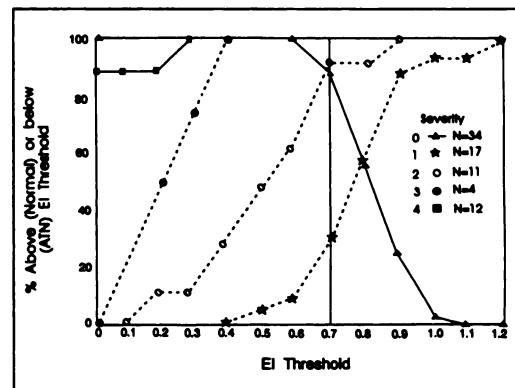
recommended threshold, the diagnostic sensitivity of  $R_{20/3}$  is shown in Table 2.

## DISCUSSION

At this clinic, the status of a transplanted kidney is monitored by radionuclide function studies at frequent intervals during any acute problem, sometimes as often as every 2 or 3 days. A tubular agent ( $^{99m}\text{Tc-MAG3}$  or  $^{131}\text{I-OIH}$ ) is used. The progress of disease and its response to therapy are revealed by quantitative changes in ERPF and EI. These methods have been used routinely at this center for nearly 20 yr and are well accepted by the clinical staff. The two measures are complementary. ERPF is a clearance measurement, and the EI, a measure of transit time, tends to reflect filtration fraction. The glomerular filtration rate is not routinely measured. The authors' preference for imaging with tubular agents—OIH for many years and now MAG3—is based on the faster clearance, which permits accurate clearance measurements to be made in a 45-min study and on the additional information provided by the



**FIGURE 3.** Correlation between  $R_{20/3}$  and severity of ATN. Percentage of cases falling below (in case of normals) or above (in case of abnormals) specified threshold values of  $R_{20/3}$  for four different grades of disease severity. The recommended threshold of 0.8 is marked on the plot.



**FIGURE 5.** Correlation between EI and severity of ATN. Percentage of cases falling above (in case of normals) or below (in case of abnormals) specified threshold values of EI for four different grades of disease severity. The recommended threshold of 0.7 is marked on the plot.

**TABLE 2**  
Diagnostic Sensitivity of Ratio of Background-Corrected Renal Activity at 20 Minutes Divided by That at 3 Minutes in Acute Tubular Necrosis and Acute Rejection

Severity	Percentage of patients having abnormal $R_{20/3}$					
	ATN (n = 104)		AR (n = 203)		Normal (n = 64)	
	%	No.	%	No.	%	No.
0	—	—	—	—	3	2/64
1	42	12/29	53	21/39	—	—
2	87	26/30	93	82/88	—	—
3	100	29/29	100	59/59	—	—
4	100	16/16	100	17/17	—	—

ATN = acute tubular necrosis; AR = acute rejection;  $R_{20/3}$  = ratio of background corrected renal activity at 20 min divided by that at 3 min.

EI. EI serves to quantify the parenchymal retention, which is a hallmark of AR or ATN with tubular (but not glomerular) agents.

The principal disadvantage of this approach is that it is labor intensive. Measurement of the EI requires, in addition to an accurate clearance method, the collection and gamma counting of an accurately timed quantitative urine specimen, with a correction for the postvoiding residual by means of pre- and postvoid bladder images. This prolongs the duration of the camera study and adds to the laboratory work and computer processing required. A simpler method would be desirable if it yielded similar diagnostic accuracy. The  $R_{20/3}$  is such a method.

A method is needed to separate cyclosporine-induced toxicity from other causes of reduced transplant function, but the preliminary findings in a small group of patients thought to have such toxicity suggest that  $R_{20/3}$  is not the answer. The findings in cyclosporine-induced toxicity resembled those in mild AR.

EI measures the fraction of activity removed from the blood that persists for a long time (35 min) in the renal parenchyma. The  $R_{20/3}$  is a similar measure because the activity in the kidney at 3 min is proportional to ERPF. (It has been shown that MAG3 clearance is directly proportional to OIH clearance and thus to para-aminohippurate clearance (5).) The choice of 20 min was based on pilot studies that showed diagnostic accuracy to fall if a shorter time interval was used and to improve only slightly if a longer time interval was used.

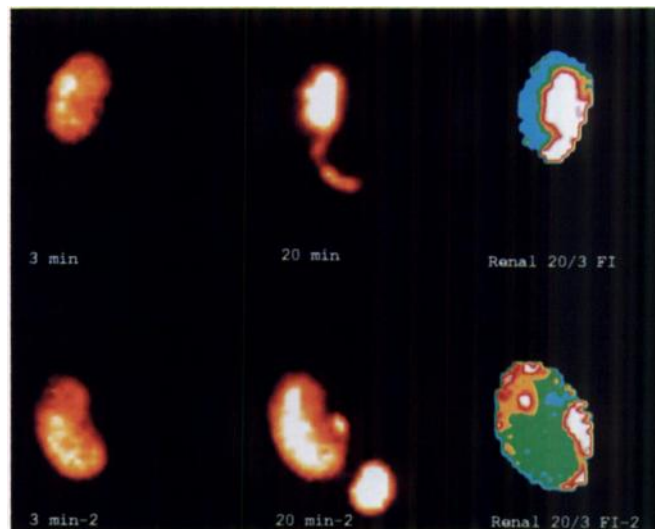
The  $R_{20/3}$  was found not only to correlate better with the clinical status than the EI, but also it was less susceptible to technical problems. Measurement of EI was technically unsuccessful in 307 of 555 cases;  $R_{20/3}$  failed in only 135 of 555.

The success rate for  $R_{20/3}$  can be further increased by functional imaging. The most common cause of failure was pelvic retention. Because the hallmark of AR or ATN is parenchymal retention, unrecognized pelvic retention would cause false-positive results. One way to deal with

this would be to use a cortical ROI rather than whole-kidney ROI. However, it is difficult to draw a cortical ROI accurately and reproducibly, and the results would be sensitive to patient motion between the 3- and 20-min images. We therefore chose a functional imaging approach instead of a cortical ROI. Functional imaging, with color coding of  $R_{20/3}$ , offers a simple means to separate the renal parenchyma from the collecting system and bladder when pelvic retention is not too great. Problems related to patient motion are readily detected. Functional imaging was found to be most useful in confirming normal function because pelvic retention was seldom a problem when ATN or AR was severe. Figure 6 shows an example of a functional image created by dividing the 1-min-long frame at 19 to 20 min by that at 2 to 3 min.

## CONCLUSIONS

1.  $R_{20/3}$  correlated closely with the clinically assessed severity of AR and ATN, more closely than did the EI.
2.  $R_{20/3}$  was effective in separating patients with moderate to severe AR and ATN from normals, more effective than the EI.
3.  $R_{20/3}$  can be measured without technical artifacts in a higher percentage of transplanted patients than can the EI. The most common technical problems with the measurement of  $R_{20/3}$  are pelvic retention and overlap of the kidney by the bladder; preliminary findings suggest that these problems can be eliminated by using functional images of the  $R_{20/3}$ .



**FIGURE 6.** Two cases in which functional images of  $R_{20/3}$  were useful. (Top row) Normal transplant with pelvic retention secondary to hydration state. Observe the normal cortical  $R_{20/3}$  (blue). The  $R_{20/3}$  calculated using a whole-kidney ROI would be invalid because of the pelvic retention. (Bottom row) Acute rejection with upper pole calyceal retention. Observe the prolonged parenchymal  $R_{20/3}$  (green). The  $R_{20/3}$  calculated using a whole-kidney ROI would be elevated, as expected with rejection, but the elevation might be falsely attributed to retained urine in the upper pole.

4.  $R_{20/3}$  is simpler to measure than the EI, requiring no urine collection, laboratory work or bladder images.

## REFERENCES

1. Dubovsky EV, Logic JR, Diethelm AG, et al. Comprehensive evaluation of renal function in the transplanted kidney. *J Nucl Med* 1975;12:1115-1120.
2. Dubovsky EV. Renal transplantation. In: Tauxe WN, Dubovsky EV, eds. *Nuclear medicine in clinical urology and nephrology*. Norwalk, CT: Appleton-Century-Crofts; 1985:233-278.
3. Russell CD, Thorstad BL, Yester MV, Stutzman M, Dubovsky EV. Quantitation of renal function with technetium-99m  $MAG_3$ . *J Nucl Med* 1988;29:1931-1933.
4. Russell CD, Palmer-Lawrence JL, Church CV, Dubovsky EV. Two measures of parenchymal retention of I-131-iodohippurate (OIH) or Tc-99m- $MAG_3$  in transplanted kidneys [Abstract]. *J Nucl Med* 1990;31(suppl): 716.
5. Russell CD, Dubovsky EV. Quantitation of renal function using  $MAG_3$  [Editorial]. *J Nucl Med* 1991;32:2061-2063.

---

## *Condensed from 15 Years Ago:*

### **Use of Technetium-99m as a Radioactive Label to Study Migratory Patterns of Leukocytes**

**Tatsumi Uchida, Toshio Nemoto, Tokuo Yui, Shin Matsuda and Shigeo Kariyone**

*Fukushima Medical College, Fukushima, Japan*

Technetium-99m has been used as a radioactive label to study the migratory patterns of neutrophils. In a previous in vitro study, neutrophils were labeled with  $^{99m}Tc$  and infused into patients with and without various hematological disorders.

Increased pulmonary localization was detected by scintillation camera within 10 min; this decreased gradually within 3 hr. Accumulation was seen in the liver and spleen at 3 hr. The same results were noted by using neutrophils labeled with  $^{99m}Tc$ -sulfur colloid. In a patient with severe ulceration in the oral cavity due to acute leukemia,  $^{99m}Tc$ -labeled transfused neutrophils collected by filtration leukopheresis were concentrated in the infected lesions.

**J Nucl Med 1979; 20:1197-1200**

---