Validation of Renal Output Efficiency as an Objective Quantitative Parameter in the Evaluation of Upper Urinary Tract Obstruction

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This is a preliminary study of the parameter, renal output efficiency (ROE), for the quantitation of furosemide (frusemide) response in diuresis renography. This is calculated by a technique independent of variations in uptake rate by the kidneys. Eleven healthy volunteers and 34 patients suspected of upper urinary obstruction were subjected to gamma camera studies using ^{99m}Tc-MAG_3 and a standard protocol. Furosemide was given at 18 min after the study was started. The ROE was calculated in each kidney and the results were correlated with final diagnosis. The range of ROE in healthy individuals varied between 82% and 98% (mean = 91.6%); while obstructed kidneys showed significantly reduced values ($p < 0.001$) ranging between 30% and 76% (mean = 56%). In the diagnosis of urinary obstruction, the ROE has a sensitivity of 91%, specificity of 94% and accuracy of 94%. ROE complements conventional diuresis renography and provides better diagnostic yield in patients with impaired renal function.

J Nucl Med 1993; 34:845–848

Renal radionuclide studies have several useful applications in the management of patients with acute or chronic urinary tract obstruction. This investigation may be necessary to establish or confirm the diagnosis of obstruction, to ascertain its site or level, to determine its extent or severity or to measure how much the obstructed kidney is contributing to total renal function. There are also other important considerations, such as monitoring renal function and urinary tract patency, following any medical or surgical intervention (*1–5*). In the differential diagnosis of urinary tract obstruction, one intervention of immense value is the use of diuretics to obtain a maximum urine flow. The principal advantage for using a diuretic is that the number of equivocal cases, especially those with nonobstructed dilated collecting systems associated with indeterminate flow curves, are substantially reduced (*6–8*). However, uncertainty still persists in kidneys with intermediate response in diuresis renograms. This is normally encountered in patients with severely impaired renal function in whom the third phase of the renogram curve does not accurately reflect radiopharmaceutical excretion from the kidneys. This is because the shape of the third phase in a renogram curve depends on the uptake, parenchymal transit and removal rate of the radiopharmaceutical by the kidneys, which vary with time in a way that ultimately depends on plasma concentration variations.

Britton and Brown (*9*) described a measurement of renal output efficiency (the isotope removal factor) using data from hippuran probe renography which related hippuran output to renal function levels. This approach was adapted by Nimmon et al. (*10,11*) to obtain renal output efficiency (ROE) in gamma camera studies using ^{99m}Tc-labeled DTPA and MAG_3. Since then, the ROE (expressed as percentage) has been in routine use in this department.

The main purpose of this study was to provide a quantitative assessment of furosemide diuretic response independent of renal function levels and to evaluate its role in the management of urinary obstruction.

MATERIALS AND METHODS

Thirty-four patients, referred to this department with a strong clinical suspicion of upper urinary tract obstruction, were included in this study. These patients had undergone gamma camera radionuclide renal studies between January 1989 and October 1991 and had a clear outcome on follow-up as assessed by the referring urologist, independent of the renal radionuclide studies. There were 15 males and 19 females aged between 20–78 yr (mean age = 46 yr) with 65 functioning renal units. One patient had a left nephrectomy and there were two nonfunctioning kidneys, which were excluded from the study for statistical analyses. A control group of eleven healthy male adults aged between 30 and 52 yr (mean age = 38 yr) were also studied.

A large field of view gamma camera was set up with a low-energy, parallel-hole, general-purpose collimator and peaked for ^{99m}Tc with a 20% window. Each patient and control received 200 ml water 30 min before the study and emptied their bladder.

Received Apr. 15, 1992; revision accepted Jan. 7, 1993.

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The subject sat reclining with his/her back to the face of the camera, which was inclined at an angle of 10–20° away from the vertical. The camera was positioned to include the left ventricle as well as the kidneys.

Each patient and control followed a standard protocol. Immediately after a bolus intravenous injection of 4 mCi (150 MBq) ^{99m}Tc-MAG$_3$, data were recorded in 10-sec frames with a 64 × 64 pixel matrix on a Micas V computer for 180 frames. Forty milligrams of furosemide (Hoechst, frusemide) was given intravenously after 18 min of study and data were collected for an additional 12 min. ROE was then determined and expressed as a percentage of the "zero output curve," the curve that would have been obtained if no activity had left the kidney, by using the analysis technique and program as described by Nimmon et al. (*10,11*). By utilizing the first 18 min of data before the administration of furosemide, deconvolution analysis with a matrix algorithm method was also employed to calculate both parenchymal and whole kidney transit time indices (*12*).

The ROE was determined as follows. Blood background subtraction was performed on each whole kidney activity/time curve (the area medial to the upper pole of each kidney) obtained from a region of interest (ROI) around the kidney outline on the 90–120-sec image. By using an iterative least squares technique, the integral of the blood clearance curve, P(t), obtained from a ROI over the left ventricle was fitted to a part of the rising second phase of the background corrected kidney curve, R(t), in accordance with the linear expression:

$$Y(t) = A + B \cdot \int P(t)\, dt,$$

where $Y(t) = R(t)$ for $t_1 \leq t \leq t_2$, A is the intercept and B is the slope of the fitted curve.

The range of data included in the fit was determined using statistical chi-squared (χ^2) and Fisher's (F) ratio parameters. Initially, data from t1 equal to 60 sec up to the peak time t2, or up to 6 min in the absence of a clearly defined peak, were used and the value of χ^2 was calculated. Points were then sequentially deleted starting at the highest data point until no significant change in χ^2 was detected as judged by the F ratio (*13*). The resultant fitted curve Y(t) corresponds to the integrated input to the kidney as a function of time. By subtraction of the background-corrected kidney curve R(t) from the integrated input Y(t), the curve O(t) representing the integrated output from the kidney was obtained. ROE is the integrated output as a percentage of the integrated input and is defined by the following equation:

$$ROE\% = [O(t)/Y(t)] \times 100\ (\%).$$

ROE percentages were correlated with the final diagnosis in each case, which was determined by the referring urologist using data from surgery, intravenous urography, ultrasonography, invasive diagnostic procedures, such as cystoscopy, micturating cystourethrography, histopathological examination, etc., and clinical follow-up and biochemical profiles of the patients. Conventional diuresis renogram curves were also independently assessed by two observers according to criteria originally described by O'Reilly et al. (*6*), as normal or nonobstructive, obstructive and indeterminate. These findings were compared with ROE in each case. Statistical analysis was done with the Student's t-test.

RESULTS

Assessment of Output Efficiency in Control Subjects

The output efficiency in 22 renal units of 11 healthy control subjects ranged between 82% and 98% (mean ± s.d. 91.6 ± 4.58). The lower limit of normal was 78% (mean ± 3 s.d.) and any value less than that was abnormal and consistent with an obstructive process in the upper urinary tract.

Assessment of Output Efficiency in Patients

ROE results in the patient group were compared with those obtained in healthy controls. The ROE in the 11 obstructed kidneys was found to be significantly reduced (56.2 ± 20.1) in comparison to healthy control subjects (91.6 ± 4.58) ($p < 0.001$), whereas there was no significant change in 52 kidneys with patent outflow tracts (93.8 ± 6.29) ($p > 0.5$). Of the total 65 functioning renal units studied, normal ROE, as per the defined criteria, was observed in 54 (range = 79%–99%, mean = 93.8%). Fifty-three of these 54 units had patent upper tracts and one had urinary obstruction at final diagnosis. Twelve renal units had abnormal output efficiency of less than 78% (range = 30%–76%, mean = 56.2%). Definite organic obstruction was demonstrated in 9 of 12 kidneys at final diagnosis, while in three the upper tracts were found to be patent (Patients 1, 2 and 7 in Table 1). Conventional diuresis renograms obtained simultaneously in all cases revealed nonobstructive patterns in 48, obstructive patterns in 10 and indeterminate or flat curves in 7. Those cases with indeterminate or flat curves were considered obstructive in the statistical analysis. A comparative statistical evaluation is given in Table 2.

DISCUSSION

Good correlation was observed between output efficiency and final diagnosis in a large majority of cases. In 54 of 65 upper tracts studied, it was possible to effectively

TABLE 1
Comparison of ROE Results and Diuresis Renography (DRG) with Final Diagnosis in Kidneys with Poor Function

Patient no.	Relative function (%)	DRG	ROE (%)	Status of upper urinary tract at final diagnosis
1	9	Indeterminate	61	No obstruction
2	13	Indeterminate	8	No obstruction
3	11	Indeterminate	40	Obstructed
4	10	Indeterminate	30	Obstructed
5	15	Indeterminate	86	No obstruction
6	9	Nonobstructive	88	No obstruction
7	11*	Indeterminate	40	No obstruction
8	89*	Indeterminate	86	No obstruction

*Patient with renal failure.

TABLE 2
Comparative Statistical Evaluation of ROE and Diuresis Renography (Subjective Evaluation) in Which All Indeterminate Results Are Obstructive

	ROE	Diuresis renogram
Sensitivity	91%	92%
Specificity	94%	89%
Accuracy	94%	89%
Positive predictive value	77%	65%
Negative predictive value	98%	98%
True-Positive	10	11*
True-Negative	51	47
False-Positive	3	6
False-Negative	1	1

*Includes two obstructive upper tracts with indeterminate curves on diuresis renography.

rule out obstruction with a negative predictive value of 98%. A false-negative result was obtained in only one instance. This patient had a stone in the lower part of the affected right ureter with mild ureteral dilatation on IVU and had good renal function (relative function = 55%). A right ureteric stone at L-4 level was surgically removed 4 days after the radionuclide study. At surgery, the ureter was found to be obstructed with moderate proximal dilatation. There is the possibility that the stone moved between the study and surgery. An obstructive pattern was also seen in one kidney with severe reflux nephropathy. ROE was found to be within normal limits (79%), thereby implying no obstruction. Patency of the upper tract was confirmed at final diagnosis.

Of the seven renal units with indeterminate curves on diuresis renography, two kidneys (Patients 7 and 8, Table 1) were from a patient with chronic renal failure (Fig. 1) with a total glomerular filtration rate (GFR) of 18 ml/min. One of the kidneys contributed 11% (GFR 2 ml/min) to the total renal function and the ROE was 40% (false-positive), while the other kidney contributed 89% to the total renal function, had a ROE of 86% and was nonobstructed, which was confirmed at final diagnosis. Of the seven renal units with indeterminate diuresis renograms,

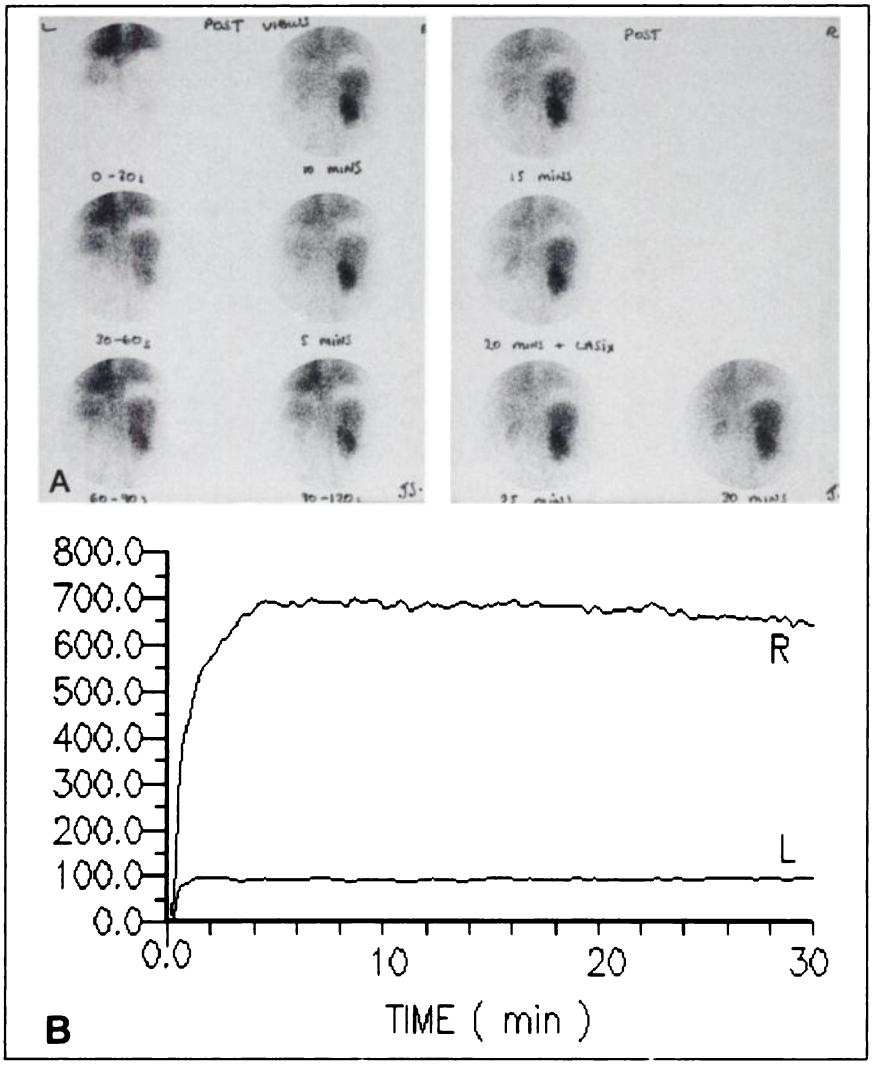

FIGURE 1. Technetium-99m-MAG3 renal study in a patient with chronic renal failure (GFR of 18 ml/min) and suspected right PUJ obstruction. (A) Posterior view renal scan sequential images obtained over 30 min. The left kidney appears small and shows severely impaired function compared to right. (B) The activity-time curve over the left kidney (L) shows an indeterminate pattern with a ROE of 46%. The right renogram (R) also shows an indeterminate pattern but has a ROE of 86%, implying a patent outflow tract which was confirmed at final diagnosis.

the output efficacy in two was significantly reduced even though there was no organic obstruction in the upper urinary tracts (Patients 1 and 2, Table 1). Both these kidneys had poor function (relative function 9% {GFR 8 ml/min} and 13% {GFR 11 ml/min} respectively). However, it is interesting to note that in the same study correct diagnosis was possible in four other kidneys with relative functions of 11%, 10%, 15% and 9%, respectively (Patients 3–6 {GFR > 12 ml/min}, Table 1). The first two kidneys (Patients 3, 4) with ROEs of 40% and 30%, respectively, had definite urinary obstruction at final diagnosis. The other two kidneys (Patients 5, 6) with ROEs of 86% and 88% had no urinary obstruction. Since ROE relates the amount excreted in response to furosemide to the amount of activity taken up by the kidney, it corrects the furosemide response for one of its major variables: the level of renal function. However, with severely impaired function, as in the renal unit no. 7 (Table 1), a false-positive result can be obtained. A large number of patients with impaired renal function need to be evaluated for GFR of individual kidneys beyond which ROE in response to furosemide becomes nonspecific.

The overall results demonstrate that in the diagnosis of urinary obstruction, the ROE parameter has a sensitivity of 91%, specificity of 94% and accuracy of 94% as compared to 92%, 89% and 89%, respectively, for conventional diuresis renograms alone (Table 2). These results, which give an apparently high sensitivity and specificity to diuresis renography, are deceptive because the indeterminate curves were considered obstructive in the statistical analysis.

In this preliminary study, the use of ROE appears to be a reasonably accurate method for the diagnosis and quantitation of the degree of upper urinary tract obstruction. ROE provides useful objective data in the serial assessment of urinary tract function and post-treatment monitoring of patients with urinary tract obstruction. Usually, an accurate assessment of upper tract function even in the presence of impaired renal function is obtainable. A larger cohort of patients with impaired renal function should be evaluated in order to assess ROE's efficacy.

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