Normalized Clearance-to-Uptake Slope Ratio: A Method to Minimize False-Positive Diuretic Renograms

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The success of diuretic renography in the evaluation of children with renal outflow tract obstruction has been hampered by a high incidence of false-positive and indeterminate results. The main causes of interpretative errors are collecting system dilatation and impaired renal function. In this prospective study, we introduce a parameter with the potential to overcome these two problems: the normalized slope ratio (SRn). This ratio is calculated from the division of the maximum renal clearance slope by the maximum renal uptake slope, both normalized to peak renal activity. Fifty-one children (94 renal units) were evaluated. Traditional parameters such as diuretic half-time and percentage of retention at 30 min showed specificities of 77% and 85%, respectively. However, the normalized clearance slope increased specificity to 94% and SRn further improved it to 98%. The SRn takes into account the renal uptake curve, whose slope is dependent on glomerular function, and thus may correct for renal dysfunction. It also differentiates obstructed from patent kidneys even in cases with significant collecting system dilatation. As shown by regression analysis, it is independent of collecting system size. We recommend the routine use of this parameter to reduce false-positive and indeterminate results of diuretic renograms.

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Hydronephrosis in children has posed a sizable problem to clinicians. In a significant number of patients, the dilated pelvicalyceal system is not obstructed (*1*). The function of these hydronephrotic kidneys may remain stable or even improve unless complications such as urinary tract infection, stone formation or acute obstruction occur (*2*). On the other hand, failure to distinguish significant obstruction from mere elasto-muscular atonicity of renal pelvis (*3*) may deprive these children of the benefits of surgery.

Diuretic renography was introduced in 1967 to identify patients with significant obstruction (*4*). Diagnostic parameters included half-time (*5*), emptying renographic patterns (*3,6*) and residual renal radioactivity at 30 min (*7*). With this methodology, however, a high percentage of false-positive and indeterminate studies were found, which raised doubts as to the usefulness of the test (*2*). Two main problems remain to be solved. First, kidneys with impaired or immature function may show a suboptimal response to diuretics and thus, produce inadequate urine output and prolonged washout times. Second, a dilated collecting system will require a larger diuretic response to clear the activity and often shows delayed washout times (*8*). These two conditions are the most common causes of false-positive results in diuretic renograms.

The Whitaker test (*9*) is invasive and employs a flow rate that may be too stressful for neonates (*10*). Controversy still exists regarding the optimal flow rate (*11*). This test is performed infrequently at our institution.

Although diuretic renography remains the most useful noninvasive diagnostic test for hydronephrosis (*8*), a technique is needed to help reduce false-positive results caused by impaired renal function and collecting system dilatation.

In this study, we introduce the normalized slope ratio (SRn), a parameter obtained by dividing the maximal slope of the diuretic clearance curve by the maximal slope of the uptake portion of the standard renogram, each normalized to maximal activity (Fig. 1). This ratio may be less affected by renal function and volume of the collecting system than other parameters. If this were true, an improvement in specificity and accuracy would be demonstrated. We used this test to evaluate 94 renal units and compared the results to those of standard half-time, clearance slope and percent retention.

METHODS

Patients

From December 1990 to April 1992, 51 children (35 boys and 16 girls) aged 1 day to 23 yr (median 13 mo) were referred for

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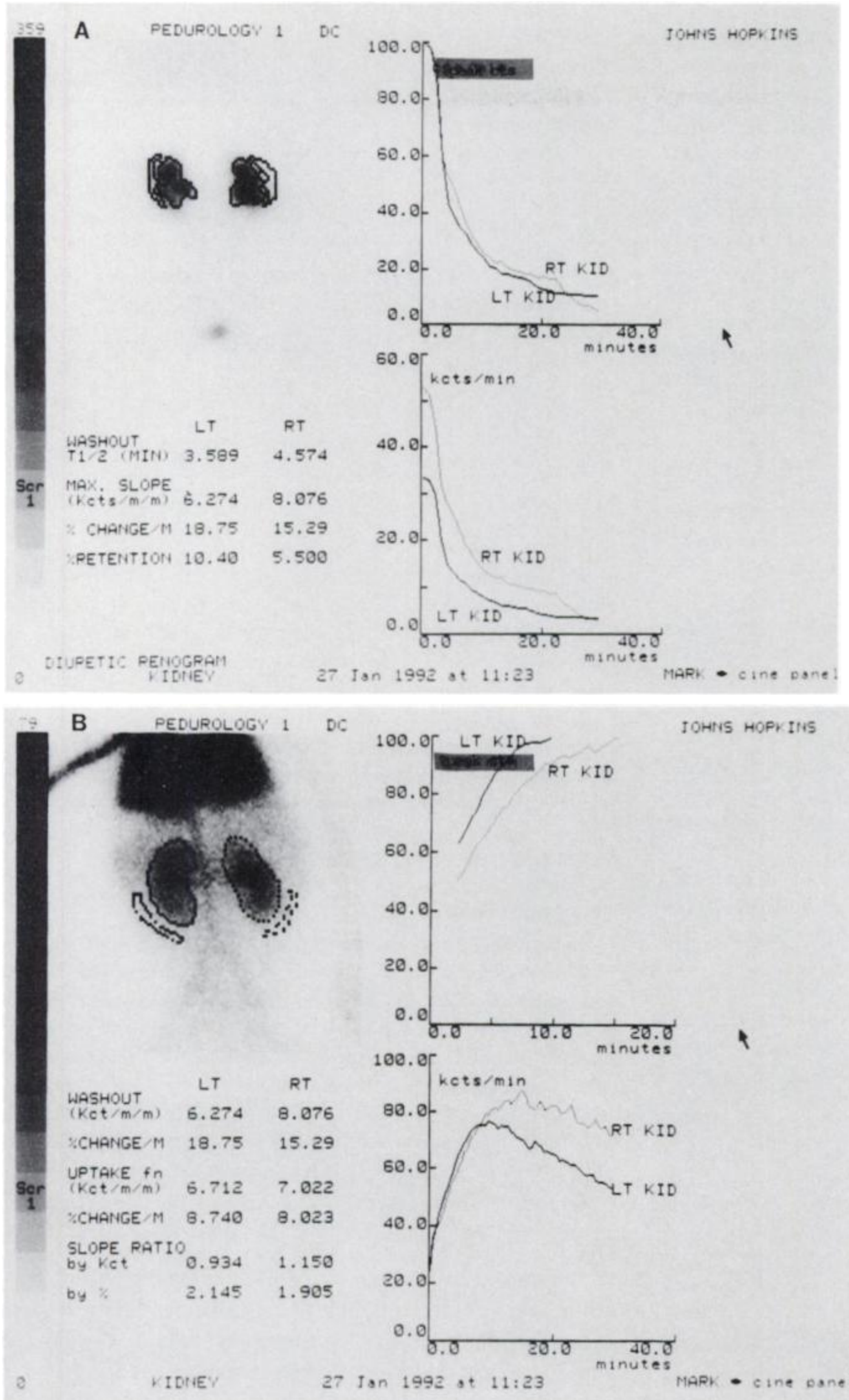

FIGURE 1. A typical computer output page of a diuretic study shows washout parameter computation (A) and washout-to-uptake ratios (B).

diuretic radionuclide renography because of hydronephrosis and suspected renal obstruction. There were 39 patients with two kidneys; 6 patients with only one kidney; 4 patients with solitary duplex kidneys in which 2 patients had upper pole nephrectomy prior to entry into study; and one patient had bilateral duplex kidneys. There was a total 94 renal units and 108 diuretic assessments were performed. Primary diagnoses are listed in Table 1. The upper moiety of one duplex kidney had virtually no function, as shown by flat uptake and washout curves, and was thus omitted from analysis.

Diuretic Renography

The patients were sedated, catheterized and closely monitored throughout the study by a nurse. After adequate hydration via oral or intravenous routes, a standard renal scan was performed for 30 min using ^{99m}Tc-DTPA at a dose of 20 mCi X

(Child's surface area/1.73 m^2) injected as an intravenous bolus. The framing rate was 1 sec/frame for 2 min and 30 sec/frame for the following 28 min. Upon confirmation of filling of the pelvicalyceal system, furosemide (1 mg/kg up to a maximum of 20 mg) was then given intravenously. Thirty 1-min posterior images were acquired on a 128 × 128 matrix using a Starcam 3000XRT (GE Medical Systems, Milwaukee, WI) with a low-energy, general-purpose collimator. Whole kidney regions of interests (ROIs) and quadrantic background ROIs were drawn on the initial renal images. After the furosemide injection, ROIs were drawn on the pelvicalyceal system and background ROIs were placed in the immediate vicinity that sometimes included parts of the renal parenchyma. Time-activity curves were generated. The program simultaneously displayed four images at different time points for ROI drawing to insure that kidneys or pelvicalyces remained within the ROI boundaries even in instances of patient motion.

Diuretic Parameters

Diuretic half-times (min) were taken as the time between peak of diuretic renogram and 50% emptying. The percentage of peak activity remaining in the pelvis at 30 min post-diuretic (RT30) was measured. The maximal clearance slope in kcts/min^2 was computed as the maxima of the first derivative curve generated from the renographic curve after Lasix administration. Normalized maximum clearance in %/min was obtained as maximum clearance slope divided by peak pelvicalyceal activity, which was converted to percentage. The washout-to-uptake ratio was calculated. The maximal uptake slope was the maxima of the first derivative curve generated from standard renograms between 2 min post-DTPA injection and peak uptake. The washout-to-uptake ratio was thus obtained as the maximal clearance slope divided by the maximal uptake slope.

SRn was computed in a similar fashion, except that the maxima of the first derivative curve generated from the uptake and washout phase of the renogram was divided by peak renal radioactivity and then converted to percentage.

The urologist's diagnoses were obtained after all numerical values of the parameters were computed. The demarcation value that produced the best separation between obstructive and nonobstructive cases and attained the highest chi square value in the "goodness of fit" test was taken as the cutoff point for individual parameters. A pilot study was performed on 20 patients (36 renal units) to roughly define the range of cutoff values. These values were then applied to the entire patient population studied.

All six parameters were tested against the urologist's final diagnosis, which combined findings from surgery, other imaging modalities, including ultrasonography (US), intravenous pyelogram (IVP), voiding cystourethrogram, nephrostogram and clinical findings during follow-up visits. The follow-up period varied from 1 to 17 mo (mean 8.9 mo).

TABLE 1
Primary Diagnoses and Level of Obstruction in Pediatric Urology Patients

Diagnoses	Number of patients
Congenital hydronephrosis	24
+ megaureters	5
Duplex kidneys	5
Primary megaureters	3
Posterior urethral valve	3
Vesicoureteric reflux	3
Prune belly syndrome	2
Multicystic kidney	2
Urethral prolapse	1
Renal vein thrombosis	1
Cross-fused ectopia	1
Cloacal anomaly	1
Total	51

TABLE 2
Diagnostic Performance of Diuretic Parameters

	Sensitivity (%)	Specificity (%)	Accuracy (%)
Half-time (min)			
>15	100	76.7	81.3
Percent tracer retention			
>40	100	84.9	87.9
Maximal clearance (kcts/min2)			
≤3	81.0	67.4	70.1
Normalized maximal clearance (%/min)			
≤4.3	100	94.2	95.3
SR			
≤0.7	100	69.8	76.6
SRn			
≤0.7	100	97.7	98.1

Statistical Analysis

Statistical analysis was performed using the BMDP (version PC90) computer statistic package. A chi square test was used to test diagnostic efficacy. Regression analysis was performed to evaluate the relationship between the parameters and degree of system dilatation. The degree of system dilatation was estimated using US, IVP or nephrostogram (0 = normal, 1 = mild, 2 = moderate, 3 = marked hydronephrosis). All cases with diuretic half-times > 30 min were arbitrarily taken as 31 in the parametric analysis. A p value < 0.05 was significant.

RESULTS

The sensitivity, specificity and accuracy of various diuretic parameters are listed in Table 2. Scatter plots showing distribution of parameter values in obstructed and nonobstructed kidneys are shown in Figure 2.

In this group of patients, the diuretic half-time had a sensitivity of 100% in detecting obstruction. Specificity, however, was 76.7%, with an accuracy of 81.3%. Percent retention at 30 min (RT30) had a better specificity of 84.9%. Maximum clearance and washout to uptake slope ratio without normalization showed much overlapping between patent and obstructed cases (Table 2).

With normalized maximum clearance, the results improved. By taking optimal demarcation at 4.3%/min, sensitivity was 100%, but the specificity increased to 94.2% with an accuracy of 95.3%. By using SRn with a cutoff

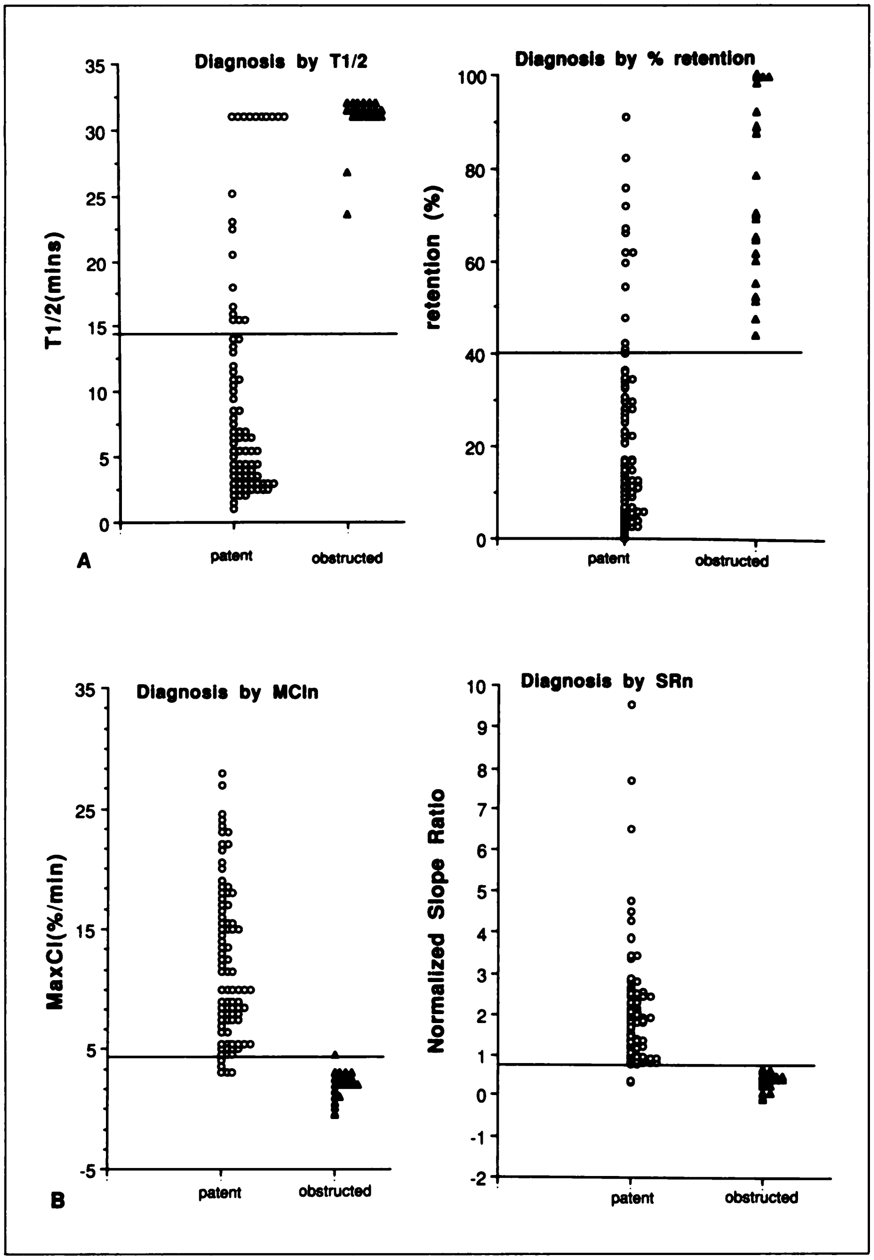

FIGURE 2. Scatter plots of various parameters in obstructed and nonobstructed kidneys: half-time and retention at 30 min (A); normalized maximum clearance and normalized washout-to-uptake slope ratio (B).

value of 0.7, sensitivity was 100% with a specificity of 97.7% and an accuracy of 98.1%.

The only false-positive for the SRn was a patient with prune belly syndrome, who showed bilateral massive dilatation of the pelvices and ureters, marked impairment of renal function and a history of vesicoureteric reflux. This patient had nonobstructive kidneys, but all diuretic renographic parameters misdiagnosed the kidneys as obstructive.

In 13 abnormally functioning kidneys without obstruction, half-time and percent retention were false-positive in six patients, however, the SRn made the correct diagnosis in all.

Aside from the two kidneys in the prune belly syndrome child, there were still six studies with half-times falling between 15 and 20 min, the indeterminate zone. Additionally, 12 other studies showed half-times > 20 min. These patients were successfully diagnosed as nonobstructed with the SRn.

Regression analysis results correlating diuretic parameters with collecting system size are listed in Table 3. Half-time, tracer retention at 30 min and maximum clearances showed significant correlation with collecting system sizes. Slope ratios were relatively independent of pelvicalyceal system size.

TABLE 3
Regression Analysis of Diuretic Parameters Versus Degree of Hydronephrosis

	Half-time	Percent retention	Normalized maximal clearance	Maximal clearance slope	SR	SRn
r	0.563	0.584	−0.227	−0.569	0.039	−0.138
p	<0.001	<0.001	0.047	<0.001	0.736	0.232

DISCUSSION

The utility of any diagnostic technique is to be found not only in its accuracy, but also in its ability to alter management choices in conditions with a potentially serious outcome.

We used diuretic renography to differentiate obstructed from patent kidneys in children with multiple urological conditions in various combinations. In this group, differentiation is crucial to management because children with anomalies such as cross-ectopia or reflux are already prone to infection and renal damage, and a superimposed obstruction, unless promptly detected and corrected, will likely aggravate the outcome.

Diuretic renography remains popular for diagnosing renal obstruction, however, although very sensitive (*10,13,14*), the specificity of this technique may be as low as 75% in children (*10*). The low specificity associated with an inordinately high rate of indeterminate results reduces its value (*2*) and may limit its role to simple exclusion of obstruction when the study is normal (*15*).

The main causes of false-positive results are poor renal function and collecting system dilatation. Diuretic washout curves are heavily dependent on renal function (*13*) and may be false-positive in patients with reduced glomerular filtration rate (GFR) or with immature renal function in the first two years of life (*2*). Parenchymal transit time indices have better specificity (*13*), but even this method may not overcome the problem because transit time is still dependent on glomerular function.

Dependence on the volume of the collecting system is another problem with diuretic washout methodology. As per the equation transit time = volume/flow, transit time is longer in a dilated system than in a normal system given the same urine flow. Diuretic renography parameters, such as half-time, percent retention and washout slopes, are strongly affected by hydronephrosis. In massive hydronephrosis, even the invasive Whitaker test is not reliable (*12*).

In this study, we used the SRn in an attempt to overcome these problems. Two slopes were calculated to derive the ratio: the maximal diuretic washout slope (the output) and the maximal renal uptake slope (the input). These slopes were normalized to maximal renal activity. Thus, the output divided by the input value produced the SRn. The normalized maximum clearance slope measures output function, which is expressed as fractional change per minute in collecting system radioactivity.

To measure the input function, we used the maximum slope of the uptake phase of the renogram, which correlates well with and is used for GFR calculation (*16*). Correction by this GFR-dependent parameter may compensate for effects of renal dysfunction and renal immaturity on diuretic washout curves. Renal dysfunction may cause flattening of the washout curve, but since it also causes flattening of the uptake curve, the ratio may not be altered.

The normalized uptake slope is also influenced by the volume of the collecting system. A hydronephrotic kidney typically takes longer to reach peak uptake, thus giving a slower rate of change and a lower normalized uptake slope. Because it is volume-dependent, the normalized uptake slope may correct the volume-dependent part of the washout curve. The SRn was shown to be independent of the degree of pelvicalyceal dilatation by regression analysis (Table 3). Table 3 also shows that other parameters, such as half-time, percent retention and maximum clearance, are influenced significantly by system dilatation.

The principle of evaluating washout in the context of the uptake was first promoted by Britton et al. (*13*). Our method represents a quantitative application of this principle. To further optimize quantification of renograms, the following additional measures were taken:

1. Background ROIs were drawn adjacent to ROIs placed strictly on the pelvicalyx of the kidney. This allowed the subtraction of activity retained in the surrounding renal parenchyma from activity in the pelvicalyceal ROI. The result is a pure assessment of changes in activity within the outflow tract. Figure 3 demonstrates the effect of parenchymal background subtraction, in that it eliminates the falsely elevated half-time and false high percent tracer retention due to slowly draining radioactivity in renal parenchyma.
2. Half-time was calculated from the peak of the diuretic renogram, taking into consideration possible delays in collecting system filling.

As listed in Table 3, maximum clearance slope is significantly affected by collecting system dilatation. Even after normalization with peak radioactivity to compensate for decreased tracer collection in the pelvicalyx by poorly functioning kidneys, the rate of washout may still be decreased, even in the absence of obstruction. Therefore, maximum clearance alone is not as reliable as SRn

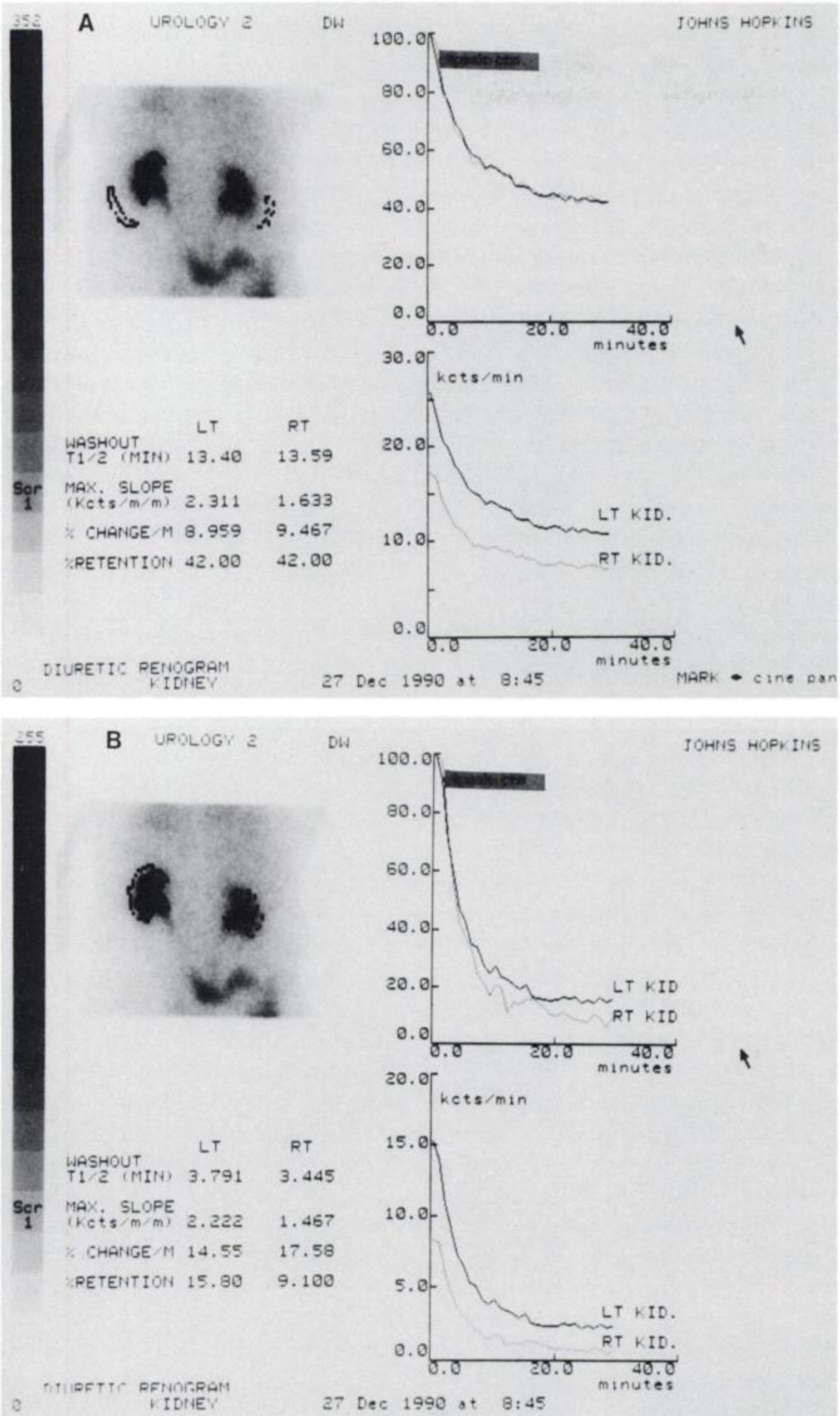

FIGURE 3. Diuretic renogram quantification in a patient with ileal urinary diversion using ordinary background subtraction (A) and parenchymal background subtraction (B).

for differentiation between obstructed and patent renal outflow systems.

Our results support the belief that SRn can minimize the rate of false-positive diuretic renograms related to renal dysfunction and hydronephrosis. In a group of complicated patients with multiple urological abnormalities, including dysfunctioning kidneys and markedly dilated collecting systems, the SRn was a better predictor of system patency or obstruction than half-time, percent retention and clearance slope. The major impact was on specificity, thus reducing the false-positive rate from 23% with half-time to 2% with SRn. The routine use of this parameter may reduce false-positive results in patients with renal dysfunction and hydronephrosis and may enhance the clinical utility of diuretic renography.

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CORRECTION

In the table of contents of the March 1993 issue of the *Journal*, the author of the continuing education article, "Artificial Intelligence: Its Use in Medical Diagnosis," is Robert Scott.