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A 7% Decrease in the Differential Renal Uptake of MAG3 Implies a Loss in Renal Function

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Abstract

OBJECTIVES—To address the fact that a decrease in the relative renal uptake of ^{99m}Tc -mercaptoacetyltriglycine (MAG3) on serial MAG3 scans may indicate a loss of function and require a change in management by providing guidance as to what constitutes a meaningful change in serial relative function measurements as well determining the normal variation of other common MAG3 renogram parameters.

METHODS—A prospective study was conducted in 24 male urology patients with stable renal function. The mean age was 66.5 ± 7.9 (SD) years; the mean serum creatinine was 1.38 ± 0.57 (SD) mg/dL, and the MAG3 renal scans were performed a mean of 11 ± 8 days apart. Each MAG3 scan included a measurement of relative function as well as the time to maximum counts and 20 minutes to maximum count ratios for both cortical and whole kidney regions of interest.

RESULTS—The Pearson and intraclass correlations for the baseline and repeat measurements of relative renal function were both 0.98. Bland-Altman plots showed no bias between the baseline and repeat relative uptake measurements. The mean difference between 2 repeated measurements of the relative MAG3 uptake was $0.04 \pm 2.88\%$ (SD) for the left kidney and $0.08 \pm 3.07\%$ (SD) for the right kidney. Comparable results were obtained for the other renogram parameters.

CONCLUSIONS—Measurements of relative renal uptake of MAG3 and common renogram parameters are highly reproducible; a decrease in relative uptake $\geq 7\%$ (ie, 50%-43%) implies a loss in renal function.

^{99m}Tc -mercaptoacetyltriglycine (MAG3) is the most widely used renal radiopharmaceutical in the United States.¹ The tracer is not filtered but is extracted by the tubules similar to para-aminohippuric acid (PAH) and I-131 orthoiodohippurate (OIH).² MAG3 renal scintigraphy is often used to determine differential renal function and evaluate renal drainage parameters. When a patient has serial MAG3 scans, the differential renal function measurements provide important information regarding stabilization or loss of individual kidney function; however, these measurements contain a critical question: How much of a decrease in differential uptake must occur before the urologist can be confident that the kidney is losing function? The reproducibility of differential function measurements has been studied in normal volunteers,³ but normal volunteers do not provide a representative sample of patients who receive serial MAG3 studies in a urology practice; results in patients, particularly those with reduced renal function, could differ from those in normal subjects.

To provide specific guidance for the urologist regarding how much of a decrease in the relative renal uptake of MAG3 must occur before the decrease implies a loss in renal function, we conducted a prospective study in 24 urology patients with stable renal function.

MATERIAL AND METHODS

Patient Population

A prospective study was conducted in 24 adult patients at the Veterans Affairs Medical Center (VAMC). The study was approved by the Institutional Review Board and informed consent was obtained. Urology patients with stable renal function were identified by members of the Urology Service and invited to participate. Because of the high preponderance of males in the VAMC patient population, all the patients participating in the study were male. The mean age of the patients was 66.5 ± 7.9 years (range 51–79). At entry, the mean serum creatinine was 1.38 ± 0.57 mg/dL (range 0.7–2.8). The normal range for serum creatinine at the VAMC is 0.5–1.2 mg/dL; 11 of 24 patients had a serum creatinine ≥ 1.3 mg/dL. MAG3 renal scans were performed a mean of 11 ± 8 days apart (range 2–29). One patient had a neobladder with reflux; in this patient, the measurement of time to maximum counts was excluded because this measurement could be affected by reflux. A technical problem prevented the calculation of the whole-kidney 20 minimum/maximum count ratio for the right kidney in a second patient. Finally, a third patient had a single left kidney; consequently, there were no renogram data for the right kidney and the relative uptake data from this patient were excluded from the relative function analysis.

Radiopharmaceutical Administration and Data Acquisition

The subjects were hydrated with approximately 500 mL of water 30 minutes before the study. Images were acquired in a 128×128 matrix with a 40-cm field-of-view General Electric, Apex, SP-4 gamma camera (Milwaukee, WI) fitted with a low-energy all-purpose collimator and data were processed on a General Electric XPert computer. Each study was performed with 1.1–1.7 mCi (41–63 MBq) of ^{99m}Tc -MAG3 (Covidien, Mansfield, MA), with the exception of one study in which the subject received 8.1 mCi (300 MBq). Each subject was imaged supine with the kidneys and bladder within the field-of-view. After the intravenous injection of ^{99m}Tc -MAG3, serial 2-second/frame digital images were obtained for the 240 seconds, followed by 80 15-second/frame images for a total study duration of 24 minutes. Time zero was defined as the 2-second interval in which the dose reached the kidney.

Dose Infiltration

Dose infiltration was calculated by drawing a region-of-interest (ROI) over the injection site at the conclusion of the study. Counts in the ROI were corrected for decay and divided by dose injected to obtain a conservative estimate of the infiltrated dose. One subject had an infiltrated dose of 98% and data were excluded from analysis, with the exception of relative uptake because that result would not be affected by infiltration.

ROI Assignment and Background Correction

ROIs were semiautomatically assigned over each kidney, with modification of the kidney ROI by the operator if necessary. Cortical ROIs were automatically defined by selecting a 2-pixel-wide area of renal parenchyma adjacent to the lateral margin of each kidney ROI; this cortical ROI was manually modified, if indicated, to exclude any tracer retained in a dilated calyx. An automated peri-renal background ROI was subsequently generated using the kidney ROI as a template. The counts/pixel in the background ROI were normalized to the

number of pixels in the whole kidney and cortical ROIs, respectively, and subtracted from counts in the kidney ROI to determine the background-corrected counts.

Measurements of Relative Function and Renogram Indexes—The relative renal uptake of MAG3 was calculated based on the integral of the background corrected counts in each kidney from 1.0–2.5 minutes postinjection. The time to peak counts and the 20minimum-to-maximum count ratios were calculated for both the whole kidney and cortical ROIs.

Statistical Analysis

To describe the reproducibility of measurements, the measurement error was calculated as error = second measurement – first measurement; this difference is called “error” throughout this paper. The distribution of error is described via the mean and the standard deviation (SD). Since any value beyond $1.96 \times SD$ is considered unlikely, any value beyond this number can be considered as a measurable true change from the baseline. We also report the minimum and maximum as well as the 5% and 95% percentiles of the error distribution. To quantify the subjects within and between variation in the data, we used a random effects model.⁴

The percentage change from baseline was calculated as error/baseline value. The paired *t*-test was used to test the null hypothesis that the mean change is zero. Rejection of this hypothesis indicates that there is a significant systematic bias. The correlations between the first and second measurements were calculated. To address the clinical question of change compared with baseline, modified Bland-Altman plots were calculated relating the percentage change in relative function between the first and second measurements to the first (baseline) measurement.⁵

RESULTS

The standard deviations of the relative function values (and other parameters) are relatively large because the subject population was heterogeneous and included patients with normal and elevated serum creatinine. Figure 1 (A, B) show the scatter plots comparing the first and second relative function measurements of the left and right kidneys, respectively. Bland-Altman plots comparing the percentage change between the first and second measurements to the first measurement showed no evidence of bias (Fig. 2). When the results in the 13 patients with normal serum creatinine were compared with those in the 11 patients with elevated serum creatinine, there was no difference in the mean error in relative uptake in the right kidneys ($P = .4$) or the left kidneys ($P = .4$), indicating that the measurement is equally reliable in both populations.

The Pearson correlations between repeated measurements of relative uptake were 0.98 for both kidneys (Table 1), showing a high linear correlation. The mean values for the baseline and repeat measurements of relative uptake of the left kidney were 48.4% and 48.5%, respectively (Table 1), and 51.6% and 51.6% for the right kidney, respectively; the mean error was $0.04 \pm 2.9\%$ (SD) for the left kidney and $0.08 \pm 3.1\%$ (SD) for the right kidney. There was no significant difference between the baseline and subsequent measurement (paired *t*-test, NS), indicating that there was no systematic bias. The random effects model analysis for both left and right kidneys showed that the within-person variation accounted for only 2% of the variation in the data, whereas the between-person variation of relative uptake accounted for the remaining 98%. This analysis also gave a high intraclass correlation of 0.98 for relative uptake, demonstrating excellent reproducibility.

Assuming a normal distribution, 95% of the values will fall within 1.96 SD from the mean, resulting in 95% confidence limits of $\pm 5.64\%$ for the right kidney and $\pm 6.01\%$ for the left kidney. These values are in accord with the values at the 5th and 95th percentiles, -5% and $+5\%$, respectively, for the right kidney; and -5% and $+6\%$, respectively, for the left kidney. Consequently, a change in differential function $\geq 7\%$, ie, 50/50 to 43/57, has a high degree of probability of representing a real decrease in differential function rather than simply representing a change because of physiological variation and measurement error.

There was no significant difference between the baseline and repeat values for the whole kidney and cortical time to maximum counts and the 20 minimum/maximum count ratios (Table 1; paired *t*-test, NS). The mean errors were not significantly different from zero, and Bland-Altman plots (not presented) showed no evidence of bias.

COMMENT

Evaluation of obstruction using MAG3 is not always straightforward; even with experienced readers, the diagnosis is indeterminate or equivocal in 15% of studies⁶ and determination of differential function is an important component in making or excluding that diagnosis. For example, in a patient with suspected unilateral obstruction, a relative function measurement of 50% might support observation of the patient even if the MAG3 drainage were equivocal, whereas a relative function measurement of 35% in a kidney with an equivocal drainage pattern would provide a much stronger rationale for intervention. In particular, in a patient with suspected unilateral obstruction, differential function decreasing from 50% to 40% on sequential MAG3 studies argues for intervention even if the washout pattern remains unchanged.

Differential renal function determined by the relative uptake of MAG3 is a well-recognized clinical parameter; the time to the maximum height of the renogram curve and the 20 minimum/maximum count ratio for cortical and whole-kidney ROIs have also been recommended as diagnostic aids by international consensus panels.⁷⁻¹⁰ Despite these applications, however, there are limited data evaluating the reproducibility of these MAG3 renogram parameters in patients. To determine whether a change is clinically significant, it is necessary to evaluate the combined effects of physiological and measurement variation on the reproducibility of these measurements and to conduct the study in a population that is representative of the clinical population where the test will be used.

Our results showed that a urologist can be highly confident that a change in the measurement of relative MAG3 uptake $\geq 7\%$, ie, differential uptake measurements changing from 50/50 to 43/57, represents a real change in relative renal function beyond a change that could be explained by measurement error. These results in patients complement a similar study in normal volunteers;³ in that study, 36 normal volunteers were scanned with ^{99m}Tc-MAG3 at least 2 days apart. Their data showed that a change $\geq 9\%$, ie, differential function changing from 50/50 to 41/59, was required to exceed the 95% confidence interval.

These differences are minor and can probably be explained by small technical differences between the 2 studies relating to the time interval used to make the measurement and background selection.^{3,11,12} The background ROI in Klingensmith et al's study was drawn as a square box inferior to the kidneys and lateral to the ureters.³ Subsequent studies have shown that an inferior background ROI underestimates the background correction and that the peri-renal background ROI used in our data processing is preferable.¹¹

The standard Bland-Altman analysis is calculated as the difference between the first 2 measurements divided by the mean of the 2 measurements. The mean is chosen as the denominator because it provides the best estimate of the true value. This approach provides

a good summary of agreement between 2 measurements. However, clinicians are interested in knowing if there is a change between the first and second measurement relative to the first measurement. To better evaluate this clinical need, we conducted our Bland-Altman analysis by evaluating a change compared with the baseline measurement rather than a change compared with the mean of the first and second measurement (Fig. 2A, 2B) and found no evidence of bias.

A limitation of the study is the fact that we processed the studies using a version of the QuantEM™ software that is currently only available on the GE Xpert computer system. Other commercial software systems for calculating differential renal function should obtain similar results to those reported here as long as they incorporate similar processing and quality control features, including the avoidance of dead time losses; use of an automated peri-renal background ROI; calculation of differential uptake based on the integral of background-corrected kidney counts from 1–2.5 minutes postinjection; using the bolus arrival in the kidneys as time zero; and providing validation studies to ensure there have been no coding errors in writing the software. A further limitation is the fact that all the patients in our study were males because of the demographics of the Veterans Affairs patient population; however, previous results have shown no differences in the differential function measurements between normal populations of males and females,¹¹ and we have no reason to believe that results evaluating reproducibility should vary by gender. Finally, it could be argued that results obtained in a general urology population may not be applicable to specific subsets of patients, such as those referred for computed tomography scans or those with prostate carcinoma or unilateral obstruction. We lack enough patients to analyze these subsets, but the results in normal volunteers and our results in a general urology population, including the subsets of those with and without an elevated serum creatinine support the application of these results to other subsets of urology patients. Future studies could be designed to confirm these results in specific patient populations.

Finally, changes in differential renal function need to be interpreted in the context of the clinical setting; a kidney may show a decrease in relative function if that kidney's function is stable but function increases in the contralateral kidney. This situation is more likely to occur in the pediatric rather than the adult population and could be resolved by a simultaneous global measurement of the MAG3 clearance or some other reliable measurement of absolute renal function.

CONCLUSIONS

Measurements of the time to maximum counts, 20 minimum/maximum count ratio, and differential renal up-take of ^{99m}Tc-MAG3 are highly reproducible. With optimal software implementation and appropriate quality control, a decrease in the relative renal uptake of MAG3 $\geq 7\%$ (ie, 50%-43%) implies a decrease in differential renal function. A more conservative cutoff value would be a decrease in differential function $\geq 9\%$ (ie, 50%-41%).

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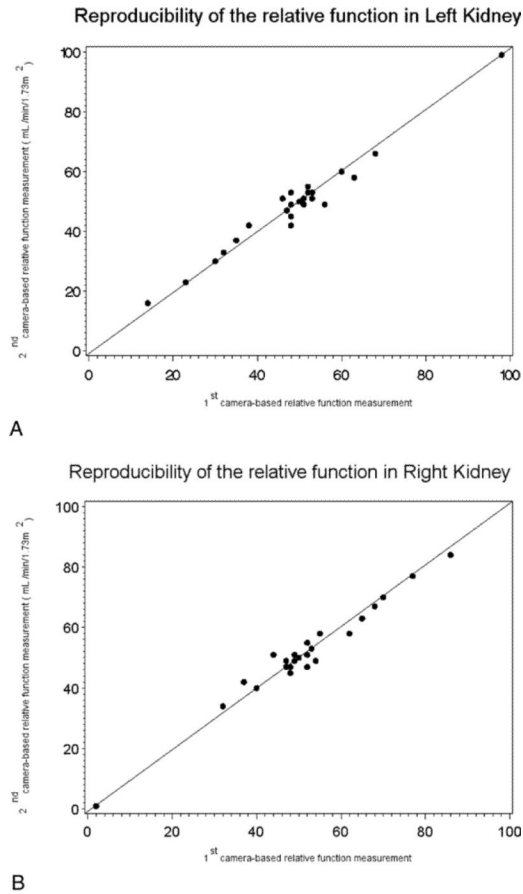
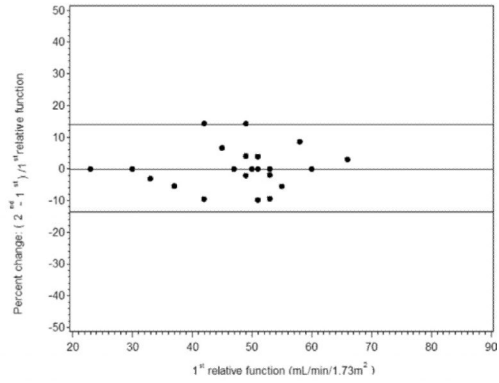


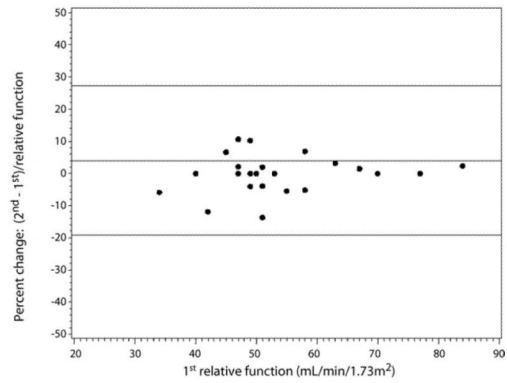
Figure 1. (A) Scatter plot and 45° line of identity displaying the close agreement of the first and second measurements of left kidney differential renal function. (B) Scatter plot and 45° line of identity displaying the close agreement of the first and second measurements of right kidney differential renal function.

Percent change in camera-based relative function Left Kidney: Bland-Altman plot



A

Percent change in camera-based relative function Right Kidney: Bland-Altman plot



B

Figure 2.

(A) Bland-Altman plots comparing the first and second differential function measurements of the left kidney show no evidence of bias. (B) Bland-Altman plots comparing the first and second differential function measurements of the right kidney show no evidence of bias.

Table 1

Reproducibility of ^{99m}Tc -MAG3 renogram parameters*

Variable	Number	1st Study	2nd Study	Error (Mean \pm 1.96 SD)	Error: 5% and 95% Percentiles	Intraclass Correlation [†]	Pearson Correlation [‡]
Right kidney (%)	24	51.6 \pm 15.8	51.6 \pm 16.3	0.04 \pm 5.64	-5, 5	0.94	0.98
Left kidney (%)	24	48.4 \pm 15.8	48.5 \pm 16.2	0.08 \pm 6.01	-5, 6	0.9	0.98
R kidney T_{max} (min)	21	3.45 \pm 0.69	3.40 \pm 0.51	-0.05 \pm 1.45	-1.2, 0.9	0.75	0.26
L kidney T_{max} (min)	21	4.10 \pm 4.10	3.76 \pm 2.78	0.30 \pm 2.82	-0.7, 0.8	0.26	0.46
R kidney 20 min/max ratio	21	0.34 \pm 0.15	0.31 \pm 0.12	-0.03 \pm 0.20	-0.28, 0.1	0.14	0.63
L kidney 20 min/max ratio	22	0.34 \pm 0.12	0.34 \pm 0.14	0.001 \pm 0.20	-0.21, 0.16	0.95	0.72
R cortical T_{max} (min)	22	2.90 \pm 0.52	2.74 \pm 0.57	-0.15 \pm 1.30	-1.3, 0.6	0.28	0.14
L cortical T_{max} (min)	22	2.75 \pm 0.64	2.75 \pm 0.57	0.014 \pm 1.02	-0.6, 0.7	0.9	0.63
R cortical 20 min/max ratio	21	0.28 \pm 0.14	0.23 \pm 0.09	-0.04 \pm 0.24	-0.28, 0.15	0.1	0.42
L cortical 20 min/max ratio	21	0.24 \pm 0.09	0.24 \pm 0.10	-0.01 \pm 0.33	-0.11, 0.2	0.67	0.4

* All P values are greater than .05 and support the null hypothesis that the mean change is zero.[†]The intraclass correlation shows the overall agreement between the first and second measurements.[‡]The Pearson correlation shows the linear correlation between the first and second measurements.