



The Journal of
NUCLEAR MEDICINE

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J Nucl Med. 1992;33:2047-2051.

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The Journal of Nuclear Medicine is published monthly.
SNMMI | Society of Nuclear Medicine and Molecular Imaging
1850 Samuel Morse Drive, Reston, VA 20190.
(Print ISSN: 0161-5505, Online ISSN: 2159-662X)

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The "Well Tempered" Diuretic Renogram: A Standard Method to Examine the Asymptomatic Neonate with Hydronephrosis or Hydroureteronephrosis

A report from combined meetings of The Society for Fetal Urology and members of The Pediatric Nuclear Medicine Council—The Society of Nuclear Medicine

Perinatal hydronephrosis (HN) and hydroureteronephrosis (HUN) are recognized more frequently as the routine use of prenatal ultrasonography increases. The decision-making process for those instances of urinary tract dilatation that require surgical correction and those that do not is based in part on the findings of diuresis renography. The methodology for performing this test has differed among nuclear medicine practitioners and the surgical findings are occasionally discrepant from the diuretic renogram interpretation. Consequently, the Society of Fetal Urology (SFU) and the Pediatric Nuclear Medicine Council (PNMC) of the Society of Nuclear Medicine met to develop by consensus a more uniform methodology. A standard method has been agreed upon for the following facets of diuretic renography: patient preparation (hydration and bladder catheterization), diuresis renography technique (radiopharmaceutical used, patient position during examination, data acquisition parameters, diuretic pharmaceutical and dosage, time of injection and regions of interest to monitor diuretic effect), and data analysis (percent differential renal function, curve pattern analysis and methods of measuring diuretic response). Pooled diuresis renogram data are being collected for analysis for correlation with surgical results and clinical outcomes to determine the most appropriate information to be derived from the diuretic renogram in neonates with HN and HUN.

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Perinatal hydronephrosis (HN) and hydroureteronephrosis (HUN) are recognized five times more frequently than in the past because of the increased use of maternal-fetal and postnatal ultrasonography (1). The primary concern in managing children with dilated upper urinary tracts is the difficulty in differentiating obstructive uropathy from nonobstructive causes of urinary tract dilatation. Radiographic imaging can aid in identifying an underlying cause such as an ureterocele, posterior urethral valves, megacalyces-megaureters or vesicoureteral reflux. These

abnormalities, however, are less frequently a cause for HN or HUN than cases where radiographic imaging does not demonstrate an anatomic defect. Thus, in the majority of patients, diuresis renography is used as a method to guide clinical management (2-6). Diuresis renography is currently the best means to assess the status of the urinary tracts for: (1) renal function and (2) the facility with which dilated pelves and ureters drain in response to a physiologic diuresis. These two parameters are believed most likely to indicate when surgery is required to optimize urinary tract drainage and preserve renal function that has been reduced by obstructive uropathy. Unfortunately, the methodology of performing diuretic renography varies among nuclear medicine practitioners and, as a result, comparisons of test results between institutions are difficult. Various pitfalls in the technique and other causes have been described which may confound test interpretation (7-9) (Table 1). With these issues in mind, members of The Society for Fetal Urology (SFU) and the Pediatric Nuclear Medicine Council (PNMC) of The Society of Nuclear Medicine have met on several occasions to agree upon the advantages and limitations of the diuresis renogram in managing neonates with urinary tract dilatation; to recognize the causes for technique differences; and to reach a consensus on the methodology whereby diuresis renography can be performed in a standardized manner. As a result of these agreements, diuresis renography is being performed in a standardized manner, and differing methods of data analysis are being examined to determine which parameters are most diagnostic for obstruction. The methods agreed upon are presented here in order to foster participation in the process of defining a standardized diuretic renogram method. This "well tempered"* renogram should provide

* cf. J.S. Bach—"The Well Tempered Clavier." In 1722, J.S. Bach published "The Well-Tempered Clavier." This collection of piano music was unique in that when Bach wrote this piece, there was no such thing as a "piano." It was called a "clavier," a forerunner of what we know as the modern piano, which was not invented until the early 1800s. At that time, "pianos" were tuned to play only in a single key. Thus, on a harpsichord tuned in "D", it would not be possible to play a piece in another key, for example, "B-flat." Andreas Werkmeister devised a system of tuning called equal temperament. Bach's collection endorsed the well-tempered tuning system, which was not universally adopted. However, the use of this system allowed musicians to perform together more easily.

Received Jun. 12, 1992; revision accepted Jun. 25, 1992.

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TABLE 1
Diuresis Renography Pitfalls*

1. Severity of obstruction
2. Variable impairments of renal function
3. Volume capacity of the pelvis, ureter or bladder
4. Hydration state
5. Bladder fullness
6. Patient positioning
7. Radiopharmaceutical
8. Region of interest
9. Patient movement
10. Dose and choice of diuretic
11. Time at which diuretic is given
12. Method of data interpretation

* Presented by M. Majd at the American Academy of Pediatrics Meeting, Chicago, IL, 1989.

the basis for comparisons with surgical and clinical results in the future.

"THE WELL TEMPERED RENOGRAM" PROTOCOL

Patient Preparation

Renal ultrasonography and voiding cystourethrography are performed prior to diuresis renography to determine if there is an anatomic cause for the HN/HUN and to determine if a megaureter is present. Other tests such as excretory urography or percutaneous manometric antegrade pyelography are also valuable in demonstrating anatomic obstruction, loss of parenchyma or a pressure gradient consistent with obstruction.

Patients entered into the protocol should be at least 1 mo of age in order to reduce the likelihood of immature renal function (10). Newborns have a lower glomerular filtration rate (GFR) than older children (11) and GFR gradually increases during the first 6 mo of life. This "immaturity" of the kidney may be reflected in the renogram pattern which characteristically demonstrates a prolongation or plateauing in the third phase. Such prolongation suggests a degree of obstruction. If renal function is immature, the kidneys may be unable to respond to diuretics well enough to assess drainage from a dilated reservoir. Premature infants should be even older than 1 mo before the initial renogram, since their renal tubular function is less likely to respond adequately to diuretics (10).

Serum creatinine is measured to confirm that there is no azotemia. If azotemia is present, more direct examination of the urinary tract by antegrade or retrograde pyelography will be needed to determine if there is a surgically correctable lesion.

Oral hydration in the form of formula or water is offered ad libitum beginning 2 hr prior to the study and throughout the study. An intravenous line (either a 25-gauge butterfly or 24-gauge intracath) is inserted for the administration of a dilute normal saline solution (D5.3NS or D5.25NS) at a rate to deliver 15 ml/kg over a 30-min

interval beginning 15 min prior to injection of the radiopharmaceutical (12,13). The infusion is continued for the remainder of the study at a maintenance fluid volume at a rate of 200 cc/kg/24 hr.

The bladder is then catheterized (after initiation of the infusion) to assure adequate drainage throughout the study. When HN is present, either a balloon retention (8 Fr.) or straight (5–8 Fr.) catheter is used. When HUN is present, a straight catheter is used in order to avoid occluding an ectopic ureteral orifice by the balloon of the retention catheter. If there is a reduced urine output despite intravenous fluid loading, or persistence scope images reveal inadequate emptying of the bladder, the catheter is repositioned and aspirated by syringe suction to keep the bladder empty. Bladder drainage during the study will reduce the absorbed radiation dose to the bladder and gonads. Furthermore, if the bladder is not permitted to fill, patient movement due to impending urination is avoided.

The diuresis of urine observed after intravenous saline loading will reflect the state of hydration and renal function. The level of diuresis may assist in determining the reliability of the test. Bladder urine drainage is measured in 10-min intervals throughout the study to determine diuretic response. Urine outputs of approximately 8 ml/kg/hr have been reported (14). We have recorded urine outputs of about 98 ml/kg/hr during diuresis in well hydrated neonates. When a diuresis is not obtained, it may be difficult to interpret the diuretic renogram.

Most neonates are probably receiving suppressive anti-septics once the diagnosis of HN/HUN is made. Patients should continue to receive these for about 3 days after catheterization.

Renography Technique

Technetium-99m-mercaptoacetyltriglycine is used (^{99m}TcMAG3, Mallinckrodt, Inc., St. Louis, MO) with an administered activity of 50 μ Ci/kg and a minimum dosage of 1 mCi. Technetium-99m-MAG3 has several potential advantages over other renal radiopharmaceuticals, including rapid renal clearance and primary excretion by the tubules upon which furosemide acts (14). In the presence of obstruction or poor renal function, the absorbed radiation dose to the patient will be reduced in comparison to other renal radiopharmaceuticals.

The renogram should be performed with the patient in the supine position. Only the heart, kidneys, ureters and bladder should be within the field of view of the gamma camera. Magnification is helpful in depicting renal anatomy and for determining the selection of regions of interest (ROI). Both digital data acquisition at 20 sec/frame and analog images are recorded. The timing of analog images may be at the practitioner's preference (i.e., 1-min images for 30 min, or 2-min, 5-min and subsequent 5-min images for 30 min). It is recommended that digital data be acquired in a 128 \times 128 matrix form for ease of ROI placement.

The methods of data analysis are critical for interpretation. The ROI for the renogram portion of the study must encompass the entire kidney, including the dilated renal pelvis. (Fig. 1A.) A ROI for background subtraction should be defined as approximately 2 pixels wide around the outer perimeter of the ROI for the kidney. The renogram time-activity curve data should be acquired for a minimum of 20–30 min.

Diuresis Phase

The diuretic pharmaceutical Furosemide (15) is injected intravenously in a dose of 1 mg/kg. Furosemide should be administered after the renogram phase (20–30 min) or when the entire collecting system is believed to be full. In the presence of decreased function or marked HN/HUN, the injection of the diuretic is delayed until the dilated renal unit is believed to be “full” or is at the peak of the renogram curve if such data are simultaneously available. Following the renogram portion of the study, the patient may be placed prone, or briefly in a sitting position, to help distribute the radioactivity more uniformly throughout the entire collecting system. The prone position ensures that the bladder lies more dependently and thereby reduces the likelihood of slowed ureterovesical drainage due to the bladder’s position. If the prone position is required to “fill” the entire system, then the diuretic study may be completed in this position.

The presence of radioactivity within the bladder is continuously monitored on the persistence scope of the scin-

tillation camera in order to determine if the bladder is kept empty. If the scintigraphic images suggest that the pelvis or ureter are incompletely drained at the termination of the diuretic renogram phase, then the child should be placed into the prone position for a subsequent image to determine if alterations in position may augment further drainage.

In the case of HN, the ROI used for diuretic time-activity curve generation should include *only* the renal pelvis and collecting system. (Fig. 1B) The ROI for background subtraction during the diuretic phase should be a transcribed semilunar area adjacent and lateral to the lower pole of the dilated collecting system. In the presence of HUN, a ROI is placed around the dilated pelvis and a separate ROI is circumscribed around the ureter to the ureterovesical junction. Computer frame rates of 20 sec are recorded. Static images at 5-min intervals for 20 min should be adequate to image the diuretic response. Thus, the combined renogram and diuretic phases of the study should take about 1 hr to acquire the necessary data.

In unilateral HN/HUN, the diuretic response should be compared with that of the diuretic response of the normal, nondilated opposite kidney. If the diuretic response in the normal kidney is also poor, it is likely that the kidneys are insufficiently mature to respond to Furosemide (10), and therefore reexamination at a later date, by the age of 6 mo, should be attempted.

Data Analysis

Percent Differential Renal Function. The total counts of the renogram curve for each kidney minus background during the interval between 60 sec and the appearance of radioactivity in the calyces are used to determine differential renal function for the entire kidney. This measure-

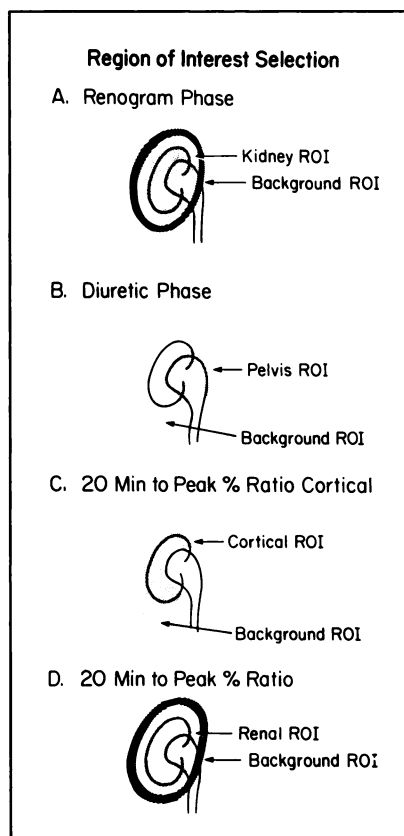


FIGURE 1. ROIs for the renogram phase (A), diuresis phase (B), 20 min to peak % ratio cortical renogram (C) and 20 min to peak % ratio determinations (D).

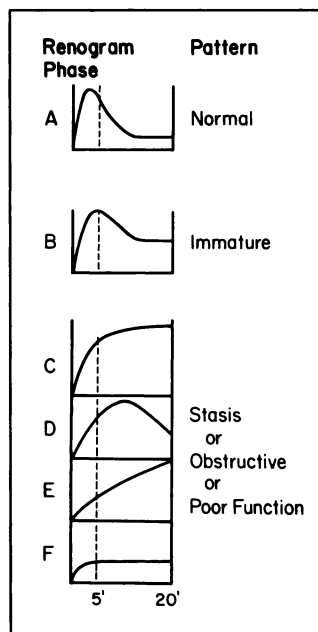


FIGURE 2. Stereotypical patterns of ^{99m}Tc-MAG3 renogram time-activity curves. Variations of the typical patterns are frequent.

ment should correspond only to the time interval when the radionuclide localizes in the tubules.

Percent Differential Cortical Renal Function. Total counts from the cortical area of each kidney (Fig. 1C) are also recorded in the interval between 60 sec to initial calyceal appearance (corrected for background). These data are used to estimate the percent differential cortical renal function.

Twenty Minutes to Peak Ratios. The counts obtained from the background subtracted renogram curves are used to calculate percent 20 min/peak ratios for the entire kidney as well as the kidney cortex for both kidneys. (Fig. 1D)

Renogram Curve Pattern Categories. Stereotypical time-activity curve patterns for the renogram phase (Fig. 2) and the diuretic phase (Fig. 3) are proposed for a standardized classification. The renogram curve patterns are characterized to suggest: normal, immature, stasis, obstructive or poor function. The diuretic curve patterns are categorized to suggest: no obstruction, indeterminate or obstruction. The patterns in each case are matched to these categories. Of course, curve patterns will vary from the stereotypical patterns shown. The best match is suggested for classification.

Categorical matches are influenced, however, by other factors which may or may not reflect obstruction. For example, an upward slope of the diuretic portion of the renogram curve suggests obstruction; however, when function is poor or there is marked HN/HUN, an upward slope may simply reflect poor function in a large capacity

reservoir which requires further filling before drainage occurs.

Determination of Clearance Half-time for Diuretic Response Analysis. There are numerous methods for calculating the drainage half-time clearance ($T_{1/2}$) of radionuclide from the renal pelvis during the diuresis phase (Fig. 4). While the differently depicted values may not necessarily be useful in an individual patient, the data from these studies, when pooled and correlated with surgical and clinical outcome, should permit a better understanding of which measurement is most valid.

Likelihood of Obstruction. An analysis of the described parameters allows an interpretation of the diuretic renogram that indicates: no obstruction, indeterminate, obstruction or immature renal function (diagnosis of obstruction is not yet possible by renography). The interpretation may be confounded by the state of tonicity of the pelvis or ureter. For example, if the dilated pelvis or ureter are atonic (as in cases of prune belly syndrome), the renogram findings may be consistent with obstruction even when other tests show the pelvis or ureter to be patent and therefore nonobstructive. Similarly, if the dilated pelvis/ureter are hypertonic (as in cases of ureteropelvic junction or ureterovesical junction obstruction), the pelvis and ure-

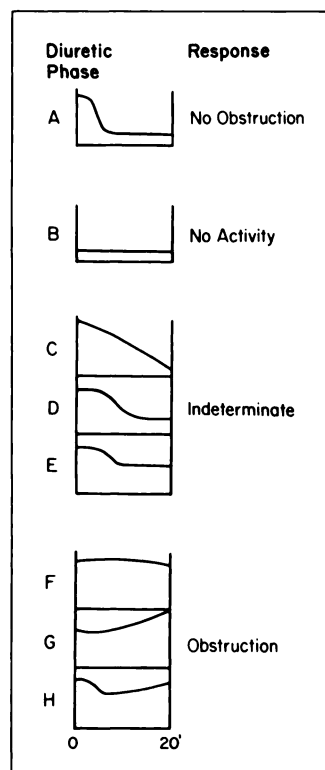


FIGURE 3. Stereotypical patterns of ^{99m}Tc -MAG3 diuresis phase time-activity renogram curves. Each of these patterns can accompany some but not all of the renogram curve patterns shown in Figure 1.

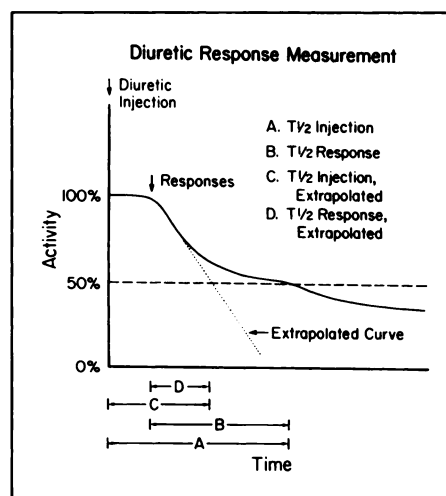


FIGURE 4. Stylized Furosemide response curve illustrates four methods of measuring the half-time clearance of the radionuclide from the collecting system of the kidney. (A) Half-time injection. The interval between the time of Furosemide injection and when there is 50% reduction of activity in the collecting system. (B) Half-time response. The interval between the time of the initial observed diuretic response (usually within 2 min after Furosemide injection) and when there is 50% reduction of activity in the collecting system. (C) Half-time injection, extrapolated. The interval between the time of injection and the time extrapolated curve from the initial observed diuretic response, which intersects with a 50% reduction of activity. (D) Half-time response, extrapolated. The interval between the time of the initial observed diuretic response and when the extrapolated curve intersects with a 50% reduction of activity. Note: other methods include a computer-derived exponential fit of the primary response and ratios of activity at differing time intervals.

ter become more muscular and are able to overcome partial resistance to provide adequate drainage, despite a luminal stenosis. This system will ultimately decompen-
sate.

Accuracy of Diuresis Renography. The accuracy of diuretic renography can only be determined by comparisons against: (1) the clinical information regarding emergence of urine infection, the clinical presentation (e.g., failure to thrive); (2) further impairments in renal function or increasingly impaired urine drainage on subsequent testing; (3) surgical findings (e.g., stenosis); (4) and/or the results of retesting after "successful" surgery. Examples of clinical outcome which show positive correlation with renography are:

1. If the renogram diagnosis is obstruction; surgery is performed and a stricture is found. If surgery is not performed, there will likely be increased HN/HUN, reduction of creatinine clearance, emergence of urine infection or hematuria.
2. If the renogram diagnosis is nonobstructive HN/HUN, it is unlikely that there will be a increased HN/HUN, loss of creatinine clearance or emergence of subsequent urine infection.

Such information has not been previously available since the correlation of clinical and diuretic renography data has been limited. The individuals who establish this protocol have charged themselves with the responsibility for appropriate follow-up in order to present the most suitable methods to increase the accuracy of diuretic renography.

CONCLUSION

The well tempered diuretic renogram protocol is rigidly designed to insure the uniformity of diuretic renography among investigators. Heretofore, there has been variability in almost all facets of the procedure. Standardization of the method will soon provide a scientific basis for understanding the appropriate usage of the diuretic renogram. The collaboration of urological and nuclear medicine practitioners will result in data which may ultimately reduce the vagaries in the management of the newborn with an obstructive uropathy.

APPENDIX

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