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Diuretic Renal Scintigraphy Protocol Considerations

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ABSTRACT

Diuretic renal scintigraphy plays a critical diagnostic role by providing a physiologic means for differentiating between obstructive and nonobstructive hydronephrosis as well as assessing the function of the affected kidney. The exam accuracy is highly dependent upon and benefits from close attention to the protocol. This article reviews kidney anatomy and physiology, patient preparation, available radiopharmaceuticals, diuretic administration, acquisition, processing, quantification, and interpretation criteria in the United States.

INTRODUCTION

The role of the kidneys is to cleanse the blood of waste and turn it into urine while also maintaining the balance of fluid and electrolytes, particularly sodium. The paired organs are located along the posterior abdominal wall, on each side of the spine, between the levels of T12 and L3. Measuring about 10-13 centimeters in length, the kidneys are bean-shaped, with their long-axis lying almost parallel to the body. The indentation of the 'bean', called the renal hilum, is oriented towards the spine. It is where arterial blood containing waste enters the kidney, cleansed venous blood exits, and urine containing waste exits. The renal parenchyma consists of an outer cortex and an inner medulla, encompassing the urine collecting system comprising calyces and the renal pelvis (FIGURE 1A). Each kidney has approximately a million small filters called nephrons within the parenchyma. Each nephron is a long, fine convoluted tubule 3-6 cm long, originating in the cortex at its glomerulus and ending in the medulla at the collecting duct (FIGURE 1B). At the end of the collecting ducts, urine containing waste passes into the calyces and is then collected in the funnel-shaped renal pelvis. The pelvis drains via the ureter to the bladder.

The normal drainage of urine can be blocked due to a wide range of congenital and acquired disorders. Obstruction to urinary outflow may, in turn, lead to increased pressure in the renal collecting system and its subsequent dilatation and swelling of the kidney (FIGURE 2). This condition, termed hydronephrosis, can lead to injury of the parenchyma and loss of function. Concern for obstruction is usually raised by detection of an elevated serum creatinine versus imaging findings of dilated renal pelvis or calyces. Occasionally, it may also be suspected in a patient undergoing follow-up after attempted correction of a previous obstruction *(1)*. Unfortunately, neither a decline in renal function nor collecting system dilation on imaging is specific for obstruction and may be due to a wide variety of nonobstructive disorders such as infection, vesicoureteral reflux, congenital anomalies, or residual changes following the resolution of a previous obstruction. Hence, in this scenario, diuretic renal scintigraphy (DRS) plays a critical diagnostic role by providing a noninvasive physiologic means for differentiating between obstructive and nonobstructive hydronephrosis as well as assessing the function of the affected kidney *(2)*. The exam is based upon the principle that under physiologic conditions, urine may be retained in a hydronephrotic renal pelvis due to one of two reasons; either due to an anatomic obstruction preventing outflow or from the reservoir effect where urine pools in the dilated renal pelvis until enough accumulates to 'spill over' into the ureter. Reservoir effect is a pseudo-obstruction that can mimic a mechanical obstruction, leading to unnecessary urologic

interventions. Diuretic renal scintigraphy takes advantage of the fact that the reservoir effect can be overcome under hi-flow conditions created with diuretic administration. By evaluating the washout of radiopharmaceutical (RP) from the collecting system and analyzing the parenchymal function, the presence of an obstruction and risk of renal damage can often be correctly assessed.

BACKGROUND

Prior to the advent of diuretic renal scintigraphy, distinguishing obstructive from nonobstructive hydronephrosis was performed by the invasive means of a pressure perfusion study, commonly known as the Whitaker test. The Whitaker test involved percutaneous kidney access via a posterior approach. A catheter was introduced into the dilated renal pelvis, and fluid was instilled at a 5-10 mL/min flow rate while the pressure was monitored in the renal pelvis and bladder *(3)*. An unobstructed renal pelvis and ureter tolerated this high flow readily, with no or only a small rise in pressure from baseline. However, if the pressure between the renal pelvis and bladder rose significantly, often greater than 15-20 cm of water, then the system was deemed obstructed *(4)*. Fortunately, in 1979, diuretic renal scintigraphy was introduced using I-131 Hippuran (ortho iodohippurate) and furosemide, offering a simpler, noninvasive means for evaluating equivocal pelviureteric obstruction *(5)(6)*. Soon thereafter, Tc99m-DTPA (diethylenetriaminepentaacetate) and Tc99m-MAG3 (mercaptoacetyltriglycine) were introduced in 1980 *(7)* and 1986, respectively *(8)*, both of which are in widespread use still today.

PREPARATION

The ability of the kidneys to significantly increase urine production in response to diuretic administration is central to the diagnostic accuracy of DRS. An increase in urine production is determined by both renal function and hydration.

To best ensure appropriate hydration, the patient should be instructed to increase fluid intake the day before and morning of the exam while avoiding natural diuretics (typically coffee, tea, and other caffeinated beverages). An additional 12 ounces of fluid with each of the 3 meals prior (totaling approximately 1 liter) to the exam is a reasonable goal. This step is contraindicated in individuals on a fluid-restricted diet, which is most commonly a treatment for congestive heart failure as well as rare disorders such as adrenal insufficiency and hyponatremia. Additionally, unlike many other nuclear medicine exams, fasting beforehand should be discouraged since this could impair efforts to pre-hydrate.

Once the patient arrives at the clinic, additional oral hydration is recommended during the 30-60 minutes immediately preceding the exam. The preferred amount of oral hydration is 5-10 mL/kg based on an international scientific committee's consensus report *(9)*, which was subsequently endorsed by the Society of Nuclear Medicine and Molecular Imaging (SNMMI) and European Association of Nuclear Medicine (EANM) *(10)*.

Patients prescribed diuretics as part of their routine medical care should be instructed to refrain from taking these medications the morning of the exam. Diuretics are most commonly prescribed for hypertension and to treat edema from heart, kidney, or liver failure. Having the patient withhold their diuretics helps ensure adequate pre-hydration while avoiding the possibility of commencing the exam during an ongoing prescribed diuresis, which can last for 6-8 hours after oral administration of furosemide *(11)*.

Additionally, though not explicitly recommended in the applicable guidelines and parameters, kidney function assessment prior to the exam can help ensure the likelihood of a diagnostic exam. As renal function decreases, urine production and responsiveness to diuretics decreases. Hence, patients with impaired renal function may not have an adequate escalation in urine flow from the standard 40 mg intravenous (IV) dose of furosemide. Therefore, the dose may need to be increased in order to achieve significant enough diuresis for diagnostic DRS results *(12)*. Fortunately, in many cases, renal function testing is obtained as part of clinical care, and the resulting serum creatinine (sCr) or estimated glomerular filtration rate (eGFR) may be used to determine an optimal diuretic dose. It is generally agreed upon that an abnormal sCr level (>1.2 ng/dL in women and >1.4 in men) usually indicates a 50% loss of renal function (i.e., GFR) and the need to increase the dose administered for DRS *(10)*.

Unfortunately, only case reports are available comparing the effectiveness of higher doses of furosemide with the standard 40 mg dose in patients with compromised renal function, and thus no evidence-based recommendations can be made *(13)*. Given this, the SNMMI-EANM recommends a simple approach of doubling the dose of furosemide to 80 mg for patients with an elevated sCr or depressed eGFR (<90 mL/min/1.73m2).

Some practices have further increased the dose to 120 mg or more in individuals with severe renal impairment (eGFR <30), given that prior research has shown that up to 171 mg may be necessary to achieve maximal diuresis when the eGFR reaches 15 mL/min/1.73m2 *(14)*. One

caveat to this approach is that individuals on chronic diuretic therapy are usually given at least the IV equivalent of their prescribed outpatient oral dose, with 1:2 being an acceptable IV to oral conversion for furosemide. The conversion for bumetanide and torsemide is 1:1 *(15)*.

The final recommended preparation step is to start an IV and have the patient void immediately prior to commencing the exam. Voiding can reduce the possibility of patient motion from discomfort or needing to terminate the study prematurely for them to urinate. It also minimizes the backpressure effect that a distended bladder may have on slowing the draining of the upper tracts *(16-19)*.

RADIOPHARMACEUTICAL

Two radiopharmaceuticals are currently in use for DRS: Tc99m-DTPA and Tc99m MAG3. Tc99m-DTPA is entirely filtered by the glomerulus, allowing it to be used to measure GFR and assess the differential or relative function of each kidney and potential outflow obstruction *(20)*. However, the kinetics of DTPA are poor in the setting of reduced renal perfusion and function, potentially leading to spurious results *(21)*. In contrast, Tc99m MAG3 predominately undergoes extraction by the tubular cells and is then secreted into the renal collecting system. Because its extraction fraction is more than twice that of DTPA, MAG3 kinetics are much less affected by impaired renal perfusion and function, providing superior image quality and making it the preferred agent 3:1 by institutions despite increased cost *(22-24)*. For this reason, Tc99m MAG3 is recommended for DRS by the SNMMI, EANM, and Society of Fetal Urology *(16)(25)(26)*.

The appropriate administered activity of MAG3 and DTPA are not clearly established. The American College of Radiology (ACR) and Society of Pediatric Radiology (SPR) document states that up to 370 MBq (10 mCi) of MAG3 and up to 555 MBq (15 mCi) of DTPA may be used *(20)*. The SNMMI-EANM procedure standard says that up to 370 MBq (10 mCi) is acceptable for either radiopharmaceutical, but 37-185 MBq (1-5 mCi) is preferred since higher administered activity is only significantly helpful when higher counts are necessary for evaluating the arterial flow of a transplanted kidney *(27)(10)*.

The recommendation for using lower administered activity was supported, in part, by a blinded comparison of DRS exams with and without the aid of the initial 1-minute flow images. The results showed no significant difference in the ability to determine if a kidney was obstructed *(28)*. Furthermore, this same paper demonstrated the diagnostic equivalence of lower (62.9

MBq (1.7 mCi)) and higher administered activity (303 MBq (8.2 mCi)) of MAG3 for determining relative/split renal function. That said, no head-to-head studies of higher (222 MBq (6-10 mCi)) versus lower (37-185 (1-5 mCi)) administered activity have been performed to confirm the SNMMI-EANM recommendation for using lower administered activity when evaluating for urine outflow obstruction. Interestingly, a recent survey of 110 US nuclear medicine labs seeking Intersocietal Accreditation Commission (IAC) accreditation showed median administered activity of 370 MBq (10 mCi) for MAG3 and 447.7 MBq (12.1 mCi) for DTPA being used for DRS. The study also revealed 10% of sites successfully use administered activity averaging 185 MBq (5 mCi) *(29)*.

DIURETIC

By far, the most commonly used diuretic for DRS is furosemide, being universally employed by 107 out of 110 sites in the study of IAC accredited nuclear medicine labs *(24)*. Furosemide is a loop diuretic, meaning it decreases sodium and chloride absorption in the kidney at the ascending loop of Henle, which in turn increases water excretion *(30)*. The recommended adult dose of IV furosemide is 0.5 mg/kg (SNMMI-EANM) versus 0.5-1.0 mg/kg (ACR-SPR), with agreement on a maximum dose of 40 mg in healthy adults. 40 mg IV of furosemide has been shown to achieve maximal diuresis in adults with normal renal function.*(10)*

When administered intravenously, furosemide has an onset of action of approximately 5 minutes and reaches peak effect starting at 15 minutes, achieving 200-300 mL of urine production within 20-30 minutes following injection *(31)*. In young, healthy adults, however, 20-30 mg may produce a diuresis sufficient for DRS and is preferred by some, given that it may avoid premature study termination in these patients due to the need to void *(10)*.

Given the average weight of U.S. adults, the 40 mg dose is suitable for the vast majority of patients without a history of renal insufficiency. However, as discussed earlier, those with decreased kidney function may benefit from an increased dose of 80 mg or higher in the setting of severe renal failure, while those on furosemide as an outpatient should receive at least as much as the IV equivalent of their prescribed oral dose. When higher doses of furosemide are being considered, particularly in elderly or fragile patients, it is important to consider the possibilities of inducing severe drops of blood pressure, including stroke. Consider discussing the use of high dose furosemide with the ordering clinician.

Though infrequently used, 1 mg IV of bumetanide, another loop diuretic, is an acceptable alternative for DRS if furosemide is unavailable *(14)*. Both furosemide and bumetanide contain a sulfonamide moiety similar to sulfur-containing antibiotics. Therefore, some practitioners prefer to avoid these drugs in patients with a known sulfa allergy and instead choose mannitol or ethacrynic acid *(32)(33)*. However, the concern for sulfur cross-reactivity has not been supported by research. A retrospective review of 88 patients with a history of sulfa-allergies and who received IV furosemide demonstrated only 2 instances of potential allergic reactions. In both cases, minor rashes were treated effectively with a single dose of diphenhydramine (Benadryl) *(34)*. Another study had similar reassuring results, showing no allergic reactions in 34 patients with a reported history of sulfa-allergies who were treated with sulfonamide containing diuretics for intracranial hypertension *(35)*. Hence, many experts now agree that these diuretics are safe for DRS in patients with a known sulfa allergy.

One of the most significant sources of debate in DRS concerns the timing of diuretic administration in relation to radiopharmaceutical administration. The ACR-SPR parameter discusses three options, the F+20 (furosemide administered 20 minutes after the radiopharmaceutical), the F+0 (furosemide and radiopharmaceutical administered simultaneously) and F-15 (furosemide administered 15 minutes before administration of the radiopharmaceutical).

The F+20 protocol is probably the most widely recognized approach, having been originally endorsed as the technique of choice by the SNMMI Pediatric Nuclear Medicine Council along with the Society of Fetal Urology *(36)*. Unfortunately, up to 25% of exams may result in equivocal results when a dilated renal pelvis empties very slowly after administration of the diuretic, preventing the exclusion of a partial obstruction *(37)*. This finding may be due to a large portion of the administered radiotracer being eliminated from the renal pelvis before the diuresis has a large enough impact on urine flow to demonstrate normal emptying *(38)*.

In an attempt to reduce the number of equivocal results, the F-15 minute approach was developed, taking advantage of the fact that maximal diuresis occurs 15-18 minutes after the IV administration of furosemide. Unfortunately, this technique has been reported to result in up to 30% of patients not completing the exam due to the need to void before the study is complete *(39)(10)*.

As a result, some experts have advocated for the F+0 protocol, a hybrid approach that shortens the procedure, reduces equivocal results, and improves patient comfort *(40)(41)*. However, the drawbacks to the early administration of diuretic (F-15 or F=0) is that it precludes the observation of natural urine drainage kinetics and, in the setting of a poorly functioning kidney, these protocols may not allow enough time for the filling of the collecting system and hence the determination of outflow obstruction.

Thus, some experts still prefer to wait until 20 minutes (or later, such as F+30 or Fmax where the diuretic is not given until it appears that the collecting system activity has reached maximum) after RP administration to give the furosemide while others have created additional protocol variants such as F+2, F+5, and F+10, all of which likely provide diagnostic results in a large percentage of cases *(10)*. Hence, it is still a matter of institutional and provider preference as to which approach is best for their patients. This preference is reflected in current practice patterns, with a total of 34 different approaches to the timing of diuretic administration in use among 107 sites undergoing genitourinary imaging accreditation with the IAC *(24)*. That said, the majority of these sites (56%) use one of 5 approaches, F=0, F+10, F+15, F+20, or F+30, with the F+20 approach being most common (21% of sites).

One final note on the subject is that recently, there has been increasing interest in a variation termed F+10sp, which performs the exam with the patient in the seated position (sp) instead of supine as recommended in the guidelines. The seated position was used in the original 1978 F+20 studies introducing DRS but was changed to supine positioning as the test became widely adopted in order to reduce patient movement and avoid the risk of a fall secondary to potential diuresis induced hypotension *(42)(43)*. The seated position takes into account the recognized importance of gravity assistance for the physiologic drainage of urine from a dilated collecting system.

ACQUISITION

For either Tc99m-MAG3 or Tc99m-DTPA, large field of view (FOV) gamma camera images (400 mm) are ideally obtained with the use of a low-energy all-purpose (LEAP) collimator or with a low-energy high-resolution (LEHR) collimator is an acceptable alternative *(20)*. A LEAP collimator is preferred because, despite the slightly lower resolution, the higher counting rates result in reduced noise for quantitative measurements, particularly when using small cortical regions of interest (ROIs) *(10)*.

Current guidelines and parameters recommend the patient be placed in the supine position with the camera at their back to take advantage of the typically posterior position of native kidneys. However, in a transplanted pelvic kidney situation, the camera should instead be located anterior *(10)(20)*. As noted, given that drainage of a dilated collecting system may be delayed in this position, even in the absence of obstruction, there is renewed interest in acquiring the exam with the patient in the seated position to allow gravity to assist *(44)*. Despite that, only 1 of the 107 sites undergoing nuclear medicine GU accreditation at the end of 2018 used the seated position *(4)*.

One topic of debate is how to address nephroptosis, a condition in which a native kidney drops down into the pelvis when standing, potentially resulting in a transient obstruction. This finding has been observed in up to 22% of individuals referred for DRS, and it may negatively impact both the measured relative function and collecting system drainage of the ptotic kidney depending on the position used during imaging *(45)*. Thus, it may be best to examine the patient twice, supine and seated, in this specific clinical scenario.

When commencing DRS, the first minute of imaging is typically acquired using 1-3 second images to assess renal arterial flow (FIGURE 3A). Starting with minute 2, all subsequent images are acquired for 15-60 seconds and are used to evaluate the parenchymal function and urine outflow from the collecting system (FIGURE 3B). This technique can be performed as either a single or two-phase acquisition depending on the timing of diuretic administration. Traditionally, if the diuretic is given before or simultaneously as the RP, a single acquisition is used. If the diuretic is administered 20 minutes or later into the study, the acquisition is typically two separate phases based upon the Santa Fe Consensus *(10)*. The first acquisition is performed for 20-30 minutes without diuretic augmentation, followed by the patient standing or walking around for a while and then voiding. If the baseline study is suspicious for obstruction, the IV diuretic is given, and an additional 20-minutes of imaging is performed *(16)*(FIGURE 4).

It should be noted that although imaging of renal perfusion using 1-3 second images of the initial RP bolus as it transits the aorta and renal arteries is typical, it has not been demonstrated to provide useful information for interpretation of DRS. Therefore, experts agree that this traditional protocol component can be omitted, simplifying both interpretation and reporting while also lowering administered activity *(28)*.

As mentioned previously, collecting system emptying can be delayed in the absence of obstruction when the patient is supine. A post-void image is recommended by both the SNMMI-EANM guideline and the ACR-SPR parameter to account for this. The image is obtained after the patient stands up, ambulates for 5 minutes, and then voids before getting back into the supine position to acquire this final image. The image should be acquired using the same time interval as the previous images (15-60 seconds) to optimize comparison *(10)*. Some experts consider the measurement of the voided urine volume helpful. At least 200 mL of urine produced over a 20-minute acquisition and 300 mL over a 30-minute acquisition indicate adequate hydration and response to the diuretic *(44)*. Despite the simple nature of this potentially helpful adjunct, none of the facilities undergoing IAC accreditation during the cycle ending 2018 included this step in their adult DRS protocol *(24)*.

PROCESSING

Time-activity curves (TACs) are generated by placing ROIs around all or portions of the kidneys. The whole-kidney (WK) ROI, which includes all of the renal parenchyma and pelvis, is necessary to assess relative function accurately. It may also be used to evaluate other parameters such as time-to-peak (Tpeak - the amount of time it takes from T=0 to reach maximum activity in the WK ROI), T-½ emptying (the time it takes for the activity in the ROI to decrease by 50% as measured from the Tpeak) and 20 minutes to max (the percent of activity remaining 20-minutes after Tpeak) (FIGURE 5A). Because this curve is affected by activity in both the parenchyma and the pelvis, an abnormality of one can give the perception of an abnormality of both. As such, a diseased cortex as seen with chronic renal failure from disorders such as hypertension or glomerulonephritis can lead to a prolonged T-½ emptying time in the absence of urine outflow obstruction, while stasis of activity in a dilated collecting system may result in a spuriously high percent 20-min/max and the appearance of cortical dysfunction.

To address problems from the WK ROI, additional ROIs may be created explicitly encompassing the renal cortex or the collecting system and their subsequent TACs used for analysis. The cortical ROI is created by delineating the cortex while excluding any activity in the pelvis and calyces, making it optimal for assessing parenchymal function parameters such as Tpeak and renal retention (FIGURE 5B). In contrast, the collecting system (CS) ROI is limited to outlining the pelvis and calyces and has been shown to allow for more accurate measurement of T-½ emptying than the WK ROI (FIGURE 5C) *(46)*.

The relative function (also called the differential renal function or split function) is the percent of renal function performed by each kidney in relation to the overall function. It is relative since it does not indicate the absolute function of each kidney (ml/min), just the percent. Hence, a kidney with 50% renal function may be healthy, but could also be poorly functioning in bilateral medical renal disease settings, such as frequently seen with long-standing diabetes. Therefore, some facilities choose to combine the DRS examination with a plasma- or camera-based clearance measurement, such as the Christensen and Groth iterative method (single sample plasma method) or the Gates method (camera-based method for DTPA) *(47)(48)*. The relative function is measured by one of two methods; either by placing a WK ROI over each kidney and measuring the integral of the counts between 1-2 minutes, 1-2.5 minutes, or 2-3 minutes after injection of the RP (deconvolution method) or by using a technique called the Rutland method, which results in a Rutland-Patlak plot. For the details of these techniques and the advantages, one is referred to the consensus report by the Scientific Committee of Radionuclides in Nephrourology *(9)*. One important note is that when using the integral method, if the diuretic is administered at the same time as the RP, then the 1-2 minute or 1-2.5 minute time periods are preferred in order to minimize the possibility of activity already having drained into the ureters and bladder and thus not being included in the WK ROI measurements, since asymmetric collecting system emptying would artifactually skew the results *(10)*.

A background correction needs to be performed to correct for activity in the ROIs that is not actually in the kidney but located in the blood, interstitial spaces and tissues superficial and deep to the kidney. To do this, a separate background ROI is created beside each kidney ROI, and it is then ‘normalized’ to account for the differences in size. The SNMMI-EANM guideline states that a perirenal background ROI, either C-shaped around the majority of the kidney or reniform-shaped completely surrounding the WK ROI, 2 pixels in thickness and 1 pixel away from the WK ROI to reduce scatter, is preferred over background rectangular or triangular shaped ROIs located superior, medial, or inferior to the whole-kidney ROI *(49)* (FIGURES 5A-C). Fortunately, automated background assignments are an acceptable approach that reduces processing time and enhances reproducibility *(10)*. When using automated background assignments, it is important to review the location of the ROIs to ensure that the ROI is not drawn outside the body.

Prior to quantification, it is important to qualitatively evaluate the TAC to assess for possible obstruction, non-obstruction, or other renal pathology. A standard, non-obstructed TAC

demonstrates a rapid uptake phase based on the renal vascular supply, then a concentration and cortical transit phase, followed by an exponential excretion phase through the renal collecting system (left kidney in FIGURE 4A). Suspicion for obstruction can be seen in a TAC that flattens following the peak, continues to rise throughout the TAC (right kidney in FIGURE 4B), or demonstrates an incomplete or delayed return to baseline. The qualitative analysis should always accompany the quantitative analysis to ensure fidelity.

QUANTIFICATION

While the shape of the TACs created from the WK ROI, and cortical or CS ROIs, if used, are central to the accurate assessment of DRS, several quantitative values have been recognized as helpful in determining obstruction and risk of future renal function decline.

Relative function, as discussed previously, is a measure of what percentage of the total renal function is performed by each kidney. It is calculated by comparing the area under the left and right WK TACs from anywhere between 1 and 3 minutes, with the 1 minute to 2 minutes and 30 seconds intervals preferred. Note, if the measurement is made after a significant amount of activity has passed into the ureter or bladder, the relative uptake measurement may be skewed because the initial amount of urine drainage from each kidney may not be proportional *(10)*. Normal values are between 45-55%, but many allow for greater variability and consider 40-60% the upper limits of normal for relative function. It is important to avoid the pitfall of using the cortical data for this measurement. While the cortical ROIs are optimal for other parenchymal assessments, they do not include all of the parenchyma and thus could artificially skew the results due to ROI asymmetries (FIGURE 6).

Time-to-peak (Tpeak) is a marker of parenchymal function. It should occur no later than 5 minutes after injection of the radiotracer for either MAG3 or DTPA, whether derived from the WK or cortical ROI. One source of error is related to the fact that this value is often derived automatically, with the software assigning it based upon the time of the highest point of the TAC. However, there are often significant errors in the 1st minute of the TAC during the flow-phase acquisition. This is due to the very short frame acquisitions (1-3 seconds each), which are highly prone to motion artifacts. Hence, the TAC and derived Tpeak should be reviewed and corrected appropriately (FIGURE 7).

20-min/max is a second marker of parenchymal function. No more than 35% of the activity should be remaining 20 minutes after the Tpeak, as measured using the cortical ROI *(50)*. A known pitfall is to calculate the value using the time point 20 minutes after the start of the exam instead of 20 minutes after Tpeak, leading to a spuriously high value.

T-½ emptying is an assessment of how quickly activity is leaving the collecting system. Ideally, it is obtained using the CS ROI but may also be accurately obtained from the WK ROI in the absence of significant parenchymal dysfunction. It is widely agreed upon that a value of <=10-15 minutes excludes obstruction *(51)*. That said, a prolonged T-½ emptying is NOT diagnostic of obstruction given the other factors that may negatively impact this value (dehydration, poor renal function, severe hydronephrosis, and the presence of significant backpressure from a full or non-compliant bladder).

Additional Measures

In addition to the values discussed above, some supplementary values are recommended by the SNMMI-EANM and International Scientific Committee of Radionuclides in Nephrourology (ISCORN) guidance documents for a more robust DRS interpretation *(10)(44)*. However, it is essential to note that these values were assessed using specific protocols for the timing of the diuretic injection in relation to RP administration. Thus, they cannot be universally applied to all approaches.

Post-void kidney to maximum (post-void/max) count ratio is a simple ratio that incorporates gravity into emptying assessment and provides valuable information. After the acquisition, the patient stands, walks, and then voids. Then, typically at 30 minutes after administering the RP, a supine 1-minute post-void image is acquired, and the post-void counts in the WK or CS ROI of the kidney of concern are divided by the maximum counts normalized for time *(50)*. In a study by Bao and colleagues at Emory of 18 variables, this value was most helpful for excluding obstruction *(46)*.

Tissue transit time (also called parenchymal transit time) is based on the fact that urine outflow obstruction negatively affects the function of the nephrons (obstructive nephropathy). This impairment of nephron function results in slow transit of the radiotracer through the tissue. While a prolonged tissue transit time (TTT) is not specific for obstruction, it increases the likelihood that it is present *(10)*. The simplest method for determining TTT is visual assessment based

upon the appearance of activity in the CS, which should be within 5 minutes of the RP injection. A value of 8 or more minutes is considered delayed *(52)(53)*.

Output efficiency and Normalized Residual Activity

Even with these parameters, diseased kidneys with a suboptimal response to diuretics are still a diagnostic challenge. This is because the shape of the parenchymal phase influences the shape of the CS emptying phase of the TAC.

Output efficiency (OE) was developed as a metric to help overcome the negative effect that impaired renal function has on the perceived CS drainage. OE allows for an evaluation of the amount of activity remaining in the kidney as a percentage of what entered the kidney and is derived using the integral of the heart activity curve. A value of >=82% has been shown as normal in a study of healthy individuals, though results are protocol-specific *(18)(54)*.

Normalized residual activity (NORA). Given the relative complexity of determining the OE and the need for specific processing software, a more simplified approach was developed with NORA. NORA is simply a measurement of the renal activity at a given 1-minute interval divided by the renal activity at 1-2 minutes after RP injection *(55)*. A value of <1.0 when comparing the 1-2 minute interval to the 20-21 minute interval or a value of < 0.10 when using the 1-minute interval acquired post-void 60 minutes from the exam start represents good renal drainage *(56)*. Unfortunately, this technique lacks standardization and appears to be more influenced by renal function and background selection than OE. It also necessitates an accurate assessment of when the RP reaches the kidneys *(57)*.

Despite their diagnostic utility, OE and NORA have not yet entered routine clinical practice. Neither variable appeared in the 174 adult DRS reports reviewed in a survey of IAC accredited facilities *(24)*.

CONCLUSION

Diuretic renal scintigraphy plays a critical diagnostic role by providing a physiologic means for differentiating between obstructive and nonobstructive hydronephrosis as well as assessing the function of the affected kidney. The exam accuracy is highly dependent upon and benefits from close attention paid to patient preparation, timing of diuretic, method of acquisition, processing,

quantification, and interpretation criteria (TABLE 1 & 2). Until standardized guidelines exist, it is critical that facilities ensure a consistent high-quality approach is applied that best meets the diagnostic needs of their referring providers and allows for accurate follow-up and comparison of results.

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TABLE 1: An Approach to Best Practices for Adult DRS – Patient Preparation and Acquisition

PATIENT PREPARATION	
Have the patient increase fluid intake day prior and morning of exam	*It may be optimal also to avoid natural diuretics though some experts believe the effect is less than the fluid consumed.*
Hold prescribed diuretics morning of exam	*Thiazides: hydrochlorothiazide (HCTZ), indapamide, metolazone, chlorthalidone* *Loop Diuretics: furosemide, bumetanide, torsemide, ethacrynic acid* *Potassium Sparing: amiloride, spironolactone, triamterene, eplerenone* *Carbonic Anhydrase Inhibitors: acetazolamide*
Oral hydration 30-60 minutes prior	*5-10 mL/kg* *450-900 mL : 15-30 oz : 2-4 cups for an adult weighing 200 lbs* *385-770 mL : 13-26 oz : 1.5-3 cups for an adult weighing 170 lbs*
Pre-void	*Immediately prior to the beginning of the exam*.
Acquisition	
Tc-99m MAG3 37-185 MBq (1-5 mCi) IV	*MAG3 preferred over DTPA despite cost. Lower doses adequate given the flow/arterial phase can be omitted.*
Furosemide 40 mg IV	*If patient on a higher dose of furosemide at home → increase to match.* *Consider 80-120 mg if known renal insufficiency.* sCr level >1.2 ng/dL (women) sCr level > 1.4 ng/dL (men) eGFR <90 mL/min/1.73m2 (either gender)
Acquisition & Timing of Diuretic F=0 single acquisition -- or -- F+20 two-part acquisition	*Most common source of variability.* ***F+10****,* ***F+15*** *and* ***F+30 are also*** *used by many practices. Remains actively debated/researched topic with no clear 'best' protocol for all situations.* ***F+10sp*** *is also considered a suitable technique.*
Post-Void Image	*Maximizes the pressure differential between kidneys and bladder, facilitating physiologic drainage. Ideally, allow the patient to stand and/or walk around for 5 minutes, void, and then image in the same position as examined.*

*Many of the quantitative values are dependent upon protocol and cannot be universally applied.

eGFR - estimated glomerular filtration rate, F=0 - furosemide and radiopharmaceutical administered simultaneously, F+10 - furosemide administered 10 minutes after the radiopharmaceutical, F+10sp - furosemide administered 10 minutes after the radiopharmaceutical in the seated position, F+15 - furosemide administered 15 minutes after the radiopharmaceutical, F+20 - furosemide administered 20 minutes after the radiopharmaceutical, F+30 - furosemide administered 30 minutes after the radiopharmaceutical, Tc99m DTPA – technetium99m-diethylenetriaminepentaacetate, Tc99m MAG3 – technetium99m mercaptoacetyltriglycine,

TABLE 2: An Approach to Best Practices for Adult DRS – Processing and Quantification

PROCESSING	
WK ROI	*Essential for relative function measurement. Generally adequate if normal kidney function.*
Cortical ROI	*Includes only parenchyma and not the CS and calyces. Optimal for assessing functional parameters such as 20-min/max (renal retention) and Tpeak.*
CS ROI	*Excludes the parenchyma and has been shown to better represent CS drainage → T-1/2*
Background ROI	*C-shaped or reniform, 2 pixels wide and 1 pixel away from the cortex.*
Relative (split) function	*Must be derived from WK ROIs. May measure using 2-3 minute intervals, but recommended to use 1-2 or 1-2.5 minute intervals if F=0 protocol.*
QUANTIFICATION	
Relative (split function)	*Normal 45-55%. Abnormal if <40%.*
Tpeak	*Normal < 5 minutes*
T-½ emptying	*Normal <10-15 minutes. Abnormal does NOT equate to obstruction.*
20-min/max	*Normal < 0.35 as measured 20 minutes after Tpeak*
TTT	*Should see activity in the CS by 5 minutes. >8 minutes is delayed.*
Post-void/max	*Post-void image acquired 30 minutes after start and activity compared to Tpeak activity.*
OE	*Helps overcome confounding effect of poor renal function on CS drainage assessment. Special processing software.*
NORA	*Normal <1.0 for 20-21 minute interval and < 0.10 when using the 1-minute interval acquired post-void @ 60 minutes from the exam start.*

*Many of the quantitative values are dependent upon protocol and cannot be universally applied.

CS – collecting system, NORA – normalized residual activity, OE – output efficiency, T-1/2 – time to decrease 50%, Tpeak – time-to-peak, TTT – tissue transit time, 20-min/max – 20 minutes to max, WK – whole kidney

FIGURE LEGEND

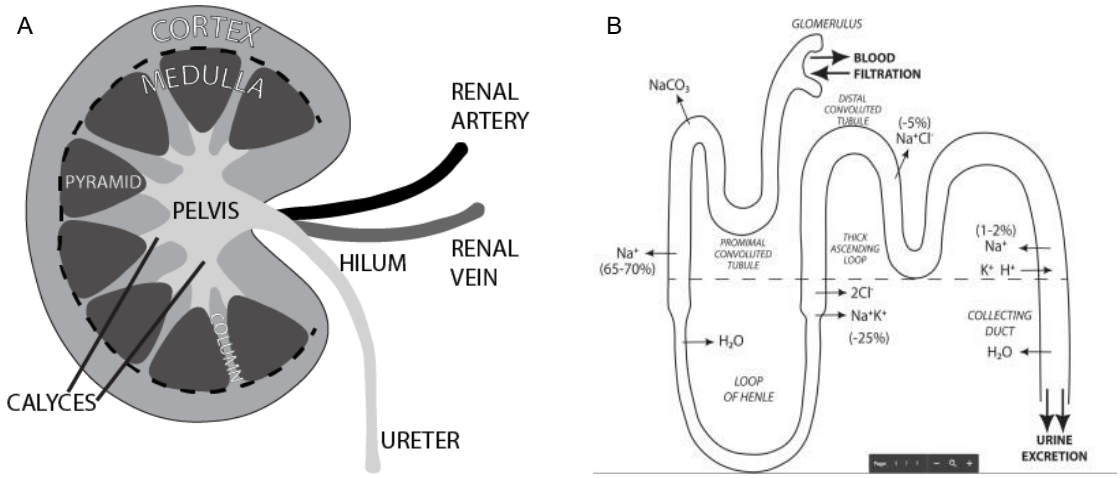

Figure 1: Kidney anatomy and glomerulus function. (A) The kidney is a bean shaped paired-organ. The indentation is called the hilum and is where the renal artery enters while the renal vein and ureter exit. The parenchyma is comprised of the outer cortex and in medulla, with the medulla further subdivided into the pyramids and columns. This all surrounds the collecting system which is made up of multiple calyces feeding into the pelvis. (B) Blood enters the glomerulus containing waste, and then leaves filtered. The nephron travels in and out of the cortex (separated by the dashed line) while electrolytes are exchanged and urine concentrated before being excreted into the calyces.

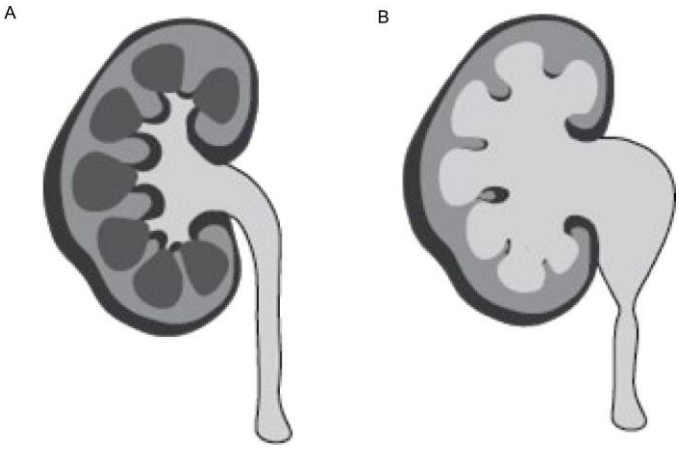

Figure 2 - (A) A normal kidney demonstrates small calyces and a decompressed renal pelvis. (B) WIth obstruction (and other disorders) the calyces and pelvis all become dilated.

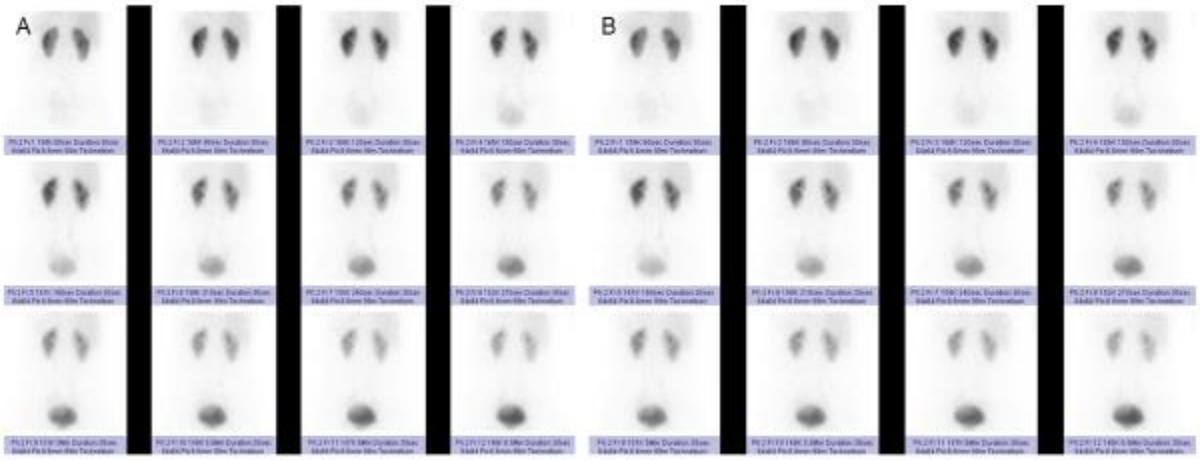

Figure 3 (A) First minute blood flow phase with frames acquired every second (first 12 seconds displayed). (B) Dynamic phase with frames acquired every 30 seconds (minutes 2-7 displayed). Phase is helpful for assessing both parenchymal function and urine drainage.

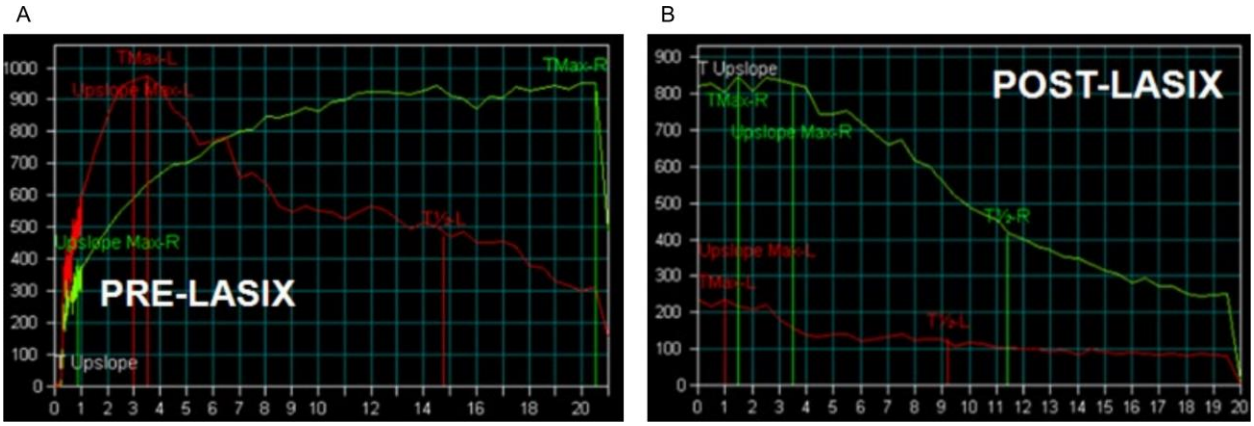

Figure 4: Dual phase acquisition. (A) First 20 minutes of findings for RIGHT kidney are concerning for obstruction, necessitating diuretic administration. (B) Post-diuretic T-½ of slightly less than 10 minutes excludes obstruction. Green curve = right kidney. Red curve = left kidney.

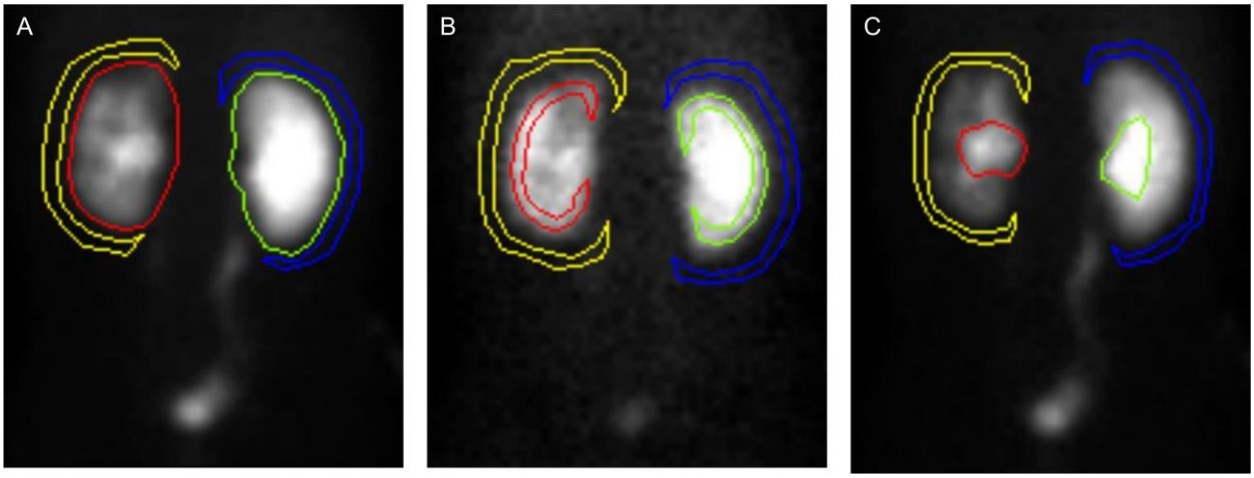

Figure 5 Kidney and background regions of interest (ROI) techniques. (A) Whole kidney ROI with peri-renal background. (B) Cortical ROI with peri-renal background. (C) Collecting system ROI with peri-renal background

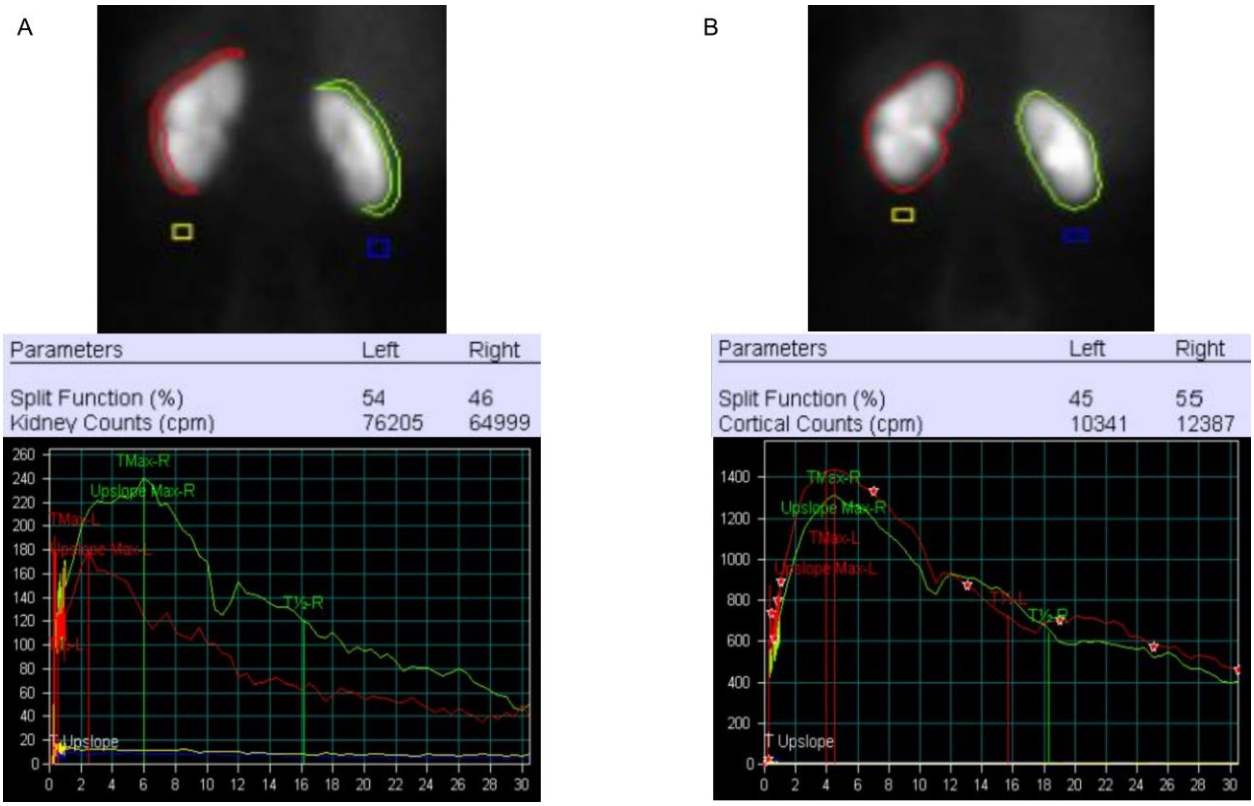

Figure 6 - Cortical versus Whole Kidney for determination of relative function. (A) cortical regions of interest, calculated relative (split) function, and cortical time activity curves. (B) whole kidney regions of interest, calculated relative (split) function, and whole kidney time activity curves. The cortical data incorrectly shows the right kidney to have decreased function compared to the left, 46% vs 54%. The correct data is shown by the whole kidney data with the right kidney having greater function than the left, 55% vs 45%, a difference of 9%.

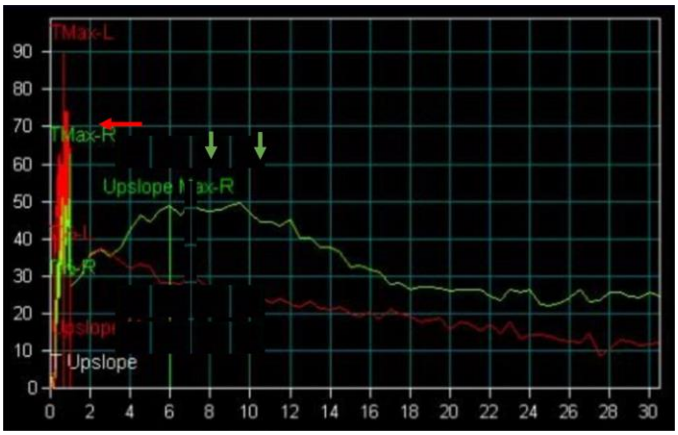

Figure 7 - Extensive motion artifact involving the 1st minute of time activity curve (TAC) representing the flow phase acquired at 1-second per frame. This results in an erroneous elevated value at 1 minute due to the ROIs overlapping vascular activity in the liver and spleen (red arrow). The actual right kidney Tpeak is delayed (>5 minutes) in the 7-9 minutes range (green arrowheads)