Clinical Application of Normalized Residual Activity as a Semiquantitative Adjunct in Assessing Renal Emptying in Pediatric Diuretic Scans

Patrick Earl A. Fernando, MD

Department of Nuclear Medicine and Theranostics, St. Luke's Medical Center - Bonifacio Global City
E-mail address: patrixx.three@gmail.com

ABSTRACT

Background:

The most recent pediatric diuretic imaging guidelines recommend the use of normalized residual activity (NORA) as a semiquantitative index of renal tracer drainage. It is defined as the ratio of post-void renal counts to 1-2 minute post-injection renal counts, with values less than 1 indicative of good drainage. We present two instances where NORA calculation was adjunctive in the evaluation of obstructive uropathy.

Case Presentation:

The first patient was a 3-month-old male with left-sided congenital hydronephrosis. On dynamic imaging, the diseased kidney showed adequate perfusion and parenchymal extraction; moderate to severe pelvicalyceal tracer retention exhibited good response to diuretic. The pre-diuretic NORA of 1.62 declined to 0.28 after furosemide challenge, concordant with imaging findings that were negative for obstruction. The second patient was a 7-week-old male, also with congenital hydronephrosis of the left kidney. Dynamic images showed the diseased kidney with diminished perfusion and function, as well as pelvicalyceal tracer retention which became more severe after the diuretic was given. The pre-diuretic NORA was 1.81, which became 1.18 post-diuretic. This inadequate decline supplemented imaging findings pointing to significant obstruction. Other semiquantitative parameters have preceded NORA; however, clearance half-time is not validated as a marker of obstructive uropathy in infants and children, and output efficiency requires specialized software to calculate. Standardization of NORA determination is largely provided for by the guidelines recommending a perirenal background region of interest, as well as minimizing the interval between starting camera acquisition and injecting the tracer.

Conclusion:

Semiquantitative analysis through NORA calculation gives relevant supporting information in the reporting of renal tracer drainage among pediatric patients. Further studies are needed to ascertain its applicability among adults and its diagnostic value in a larger sample of affected Filipino children.

***Keywords**: normalized residual activity, diuretic renal scan, congenital hydronephrosis, Tc-99m MAG3*

INTRODUCTION

In 2018, the Pediatric Imaging Council of the Society of Nuclear Medicine and Molecular Imaging (SNMMI) and the Pediatric Committee of the European Association of Nuclear Medicine (EANM) jointly released procedural guidelines for the conduct of diuretic-augmented renography in infants and children [1]. With hydronephrosis being the most commonly detected congenital anomaly of the urinary tract, the goal of imaging is to determine the functional status of the diseased kidney and, if applicable, prevent further loss of function through surgical intervention. Congenital hydronephrosis may be caused by a variety of entities, such as vesicoureteral reflux, ureteropelvic junction stenosis, and ureterovesical junction stenosis, among others. Diuretic renal scans in these group of patients not only give information on renal perfusion and function, but also determine the severity and location of obstructive uropathy when present.

As pediatric patients are not small adults, pediatric diuretic renal scintigraphy is not a carbon copy of the adult protocol. To start, Tc-99m MAG3 is preferred over Tc-99m DTPA. The extraction fraction (percentage of tracer extracted with each pass through the kidney) of

Tc-99m MAG3 is 40-50%, compared to only approximately 20% with Tc-99m DTPA [2]. This results in Tc-99m MAG3 images having better target-to-background ratios with good temporal resolution and faster renal clearance, making it conducive particularly for neonatal renography [3]. Second, tracer dose is calculated based on set guidelines by the SNMMI and EANM [4]. Third, the administered dose of furosemide is weight-based (at 1 mg/kg), rather than the mandated 40 mg dose for adults. Fourth, in drawing the background region of interest (ROI), a C-shaped ROI is preferred along the lateral aspect of the kidney, rather than a quadrilateral ROI in the inferolateral side.

The 2018 guidelines place an emphasis on gravity-assisted post-void imaging. In adults, a 1-minute static post-void image is acquired after each sequence of dynamic images (pre-diuretic and post-diuretic). Because not all pediatric patients are toilet-trained, post-void imaging can pose a challenge to perform. It is advised to acquire post-diuretic post-void images once the bladder has emptied after being kept upright for a standardized period of time (e.g. 10 to 15 minutes). The rationale of this is twofold: (a) the supine position of the patient can affect tracer excretion, and (b) insufficient renal drainage due to a full bladder at the end of dynamic imaging may yield inadequate images for interpretation, particularly in a demographic where vesicoureteral reflux is more prevalent.

Normalized residual activity (NORA) is recommended by the guidelines as the most robust measurement of post-diuretic clearance [1]. It is a semiquantitative parameter which is defined as the ratio of renal counts post-void to the renal counts on the second minute post-tracer injection. The second minute composite image is used as it is deemed to have the maximum tracer accumulation in the renal parenchyma without visualizing tracer activity in the pelvicalyceal system. As post-void images are acquired twice (pre- and post-diuretic), pre-diuretic and post-diuretic NORA values (NORApre and NORApost, respectively) can be obtained using the following formulas:

$$\mathrm{NORA_{pre}} = \frac{\text{post-void pre-diuretic counts}}{\text{2nd minute pre-diuretic counts}}$$

$$\mathrm{NORA_{post}} = \frac{\text{gravity-assisted post-void counts}}{\text{2nd minute pre-diuretic counts}}$$

In general, a NORA value less than 1 denotes good tracer drainage. In the context of post-diuretic imaging, a NORA value less than 1 implies good response to diuretic, and consequently, reduced likelihood of significant mechanical obstruction.

Pediatric renal diuretic scans are not as frequently encountered as other general nuclear imaging procedures in the local setting. This report presents two instances where NORA supplemented qualitative findings in the assessment of renal drainage.

CASE 1

A 3-month-old male with congenital hydronephrosis of the left kidney was referred to our department for diuretic-augmented renal imaging to evaluate for ureteropelvic junction obstruction. Dynamic imaging of the kidneys was performed in the posterior view for 20 minutes after injection of 29.6 MBq of Tc-99m MAG3. Sequential imaging was again done after injection of 8 mg furosemide. Gravity-assisted post-void image was obtained afterwards.

Bolus phase (Figure 1) showed good renal perfusion bilaterally. The diseased left kidney exhibited fair cortical tracer extraction, timely excretion, and moderate to severe tracer retention in the dilated pelvis (Figure 2A) which washed out after the diuretic was given (Figure 2B). The time-activity curve (Figure 3) showed an upsloping curve that only declined post-diuretic. The right kidney had good parenchymal and excretory function, with complete radiotracer washout after furosemide was administered; no discrete abnormality was detected in the time-activity curve.

Kidney counts were extracted by producing composite images at three time points: (a) 60-120 seconds after tracer injection, i.e. the second minute of dynamic imaging; (b) the 1-minute static post-void image right before the diuretic was injected; and (c) the 1-minute static gravity-assisted post-void image at the end of diuretic-augmented imaging. Regions of interest were drawn around the kidneys, with C-shaped background ROIs along the lateral aspects (Table 1). The background-corrected counts were then used to calculate for pre-diuretic and post-diuretic NORA values (Table 2).

FIGURE 1. Perfusion images of the 3-month-old patient

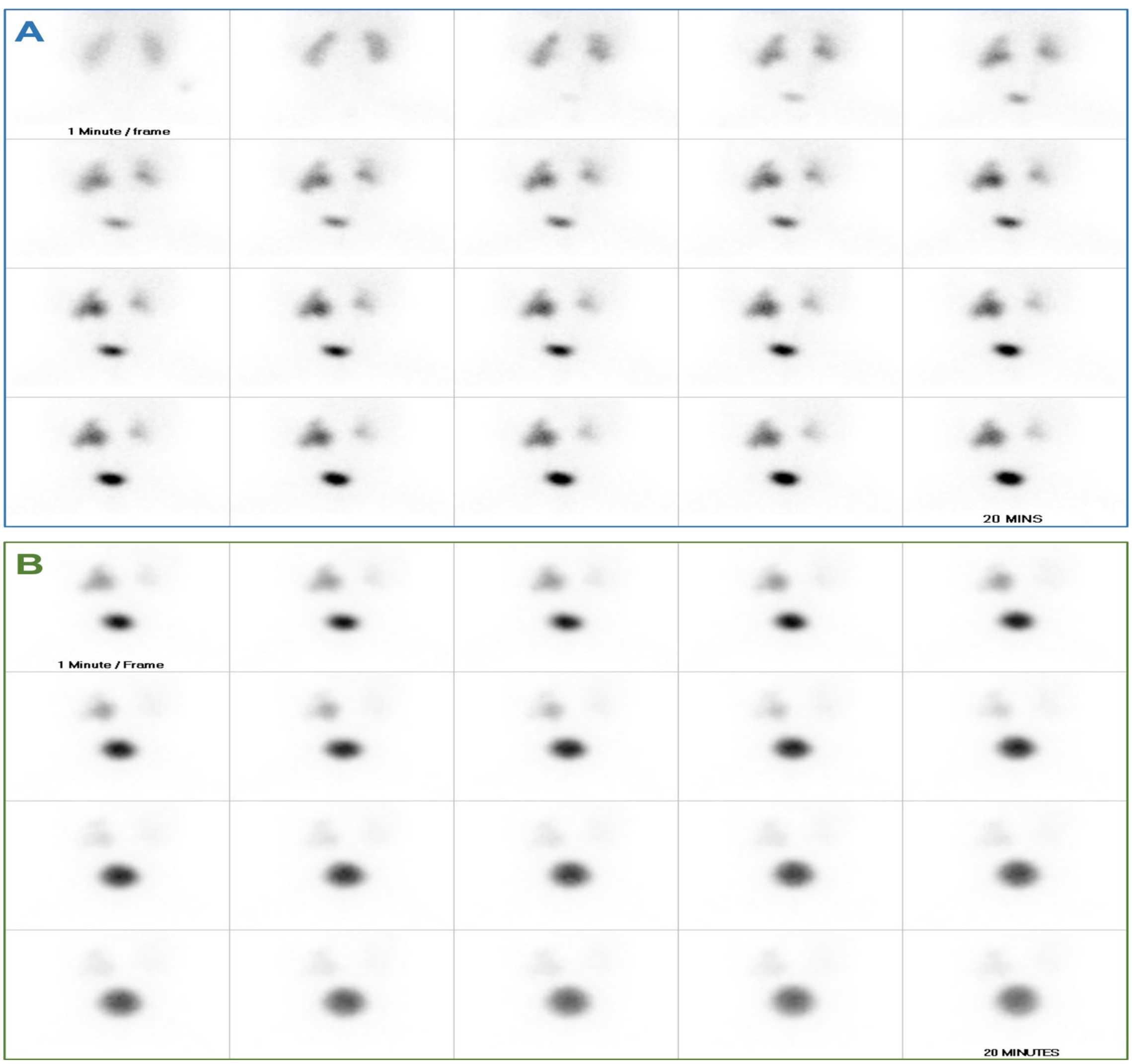


FIGURE 2. 20-minute pre-diuretic (A) and post-diuretic (B) dynamic images of the 3-month-old patient

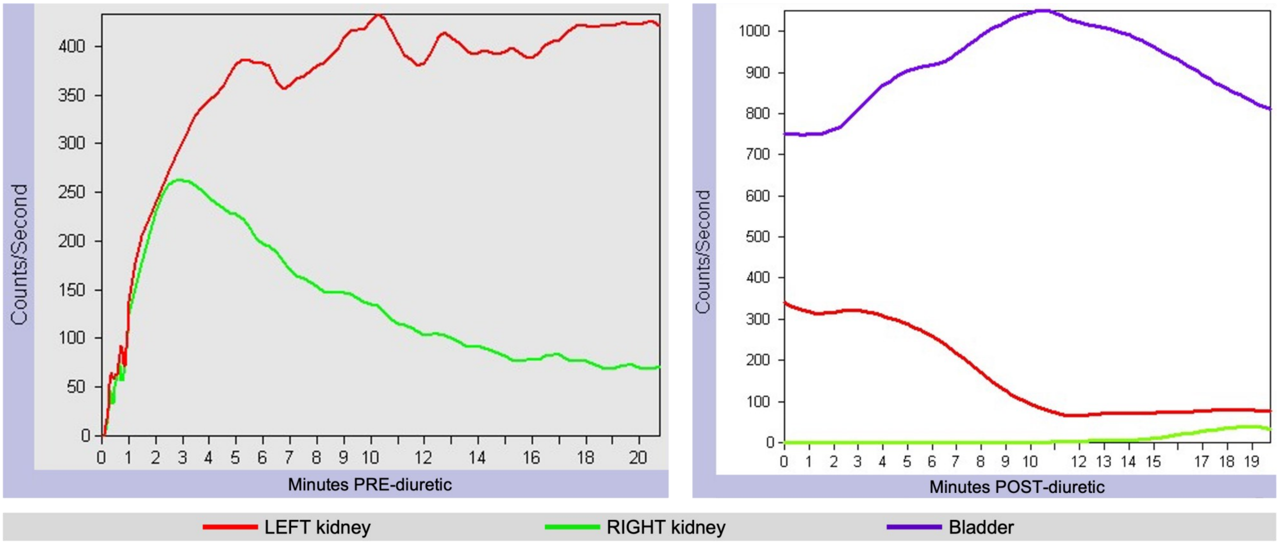


FIGURE 3. Pre- and post-diuretic time-activity curves of the 3-month-old patient

TABLE 1. .Image processing and number of counts were obtained to calculate pre- and post-diuretic NORA values for the 3-month-old patient. Reported kidney counts are after background correction.

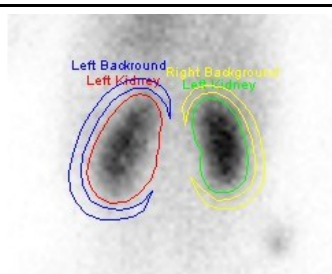
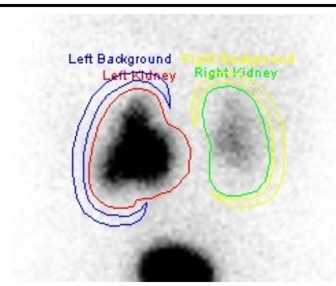
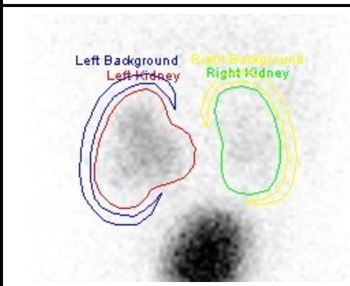
	2ND MINUTE POST-INJECTION	PRE-DIURETIC POST-VOID	POST-DIURETIC *(GRAVITY-ASSISTED)* POST-VOID
Image			
Left kidney counts	18759	30375	5160
Right kidney counts	16320	5802	1636

TABLE 2. . Differential renal function and calculated NORA values for the diuretic scan of the 3-month-old patient

	LEFT KIDNEY	RIGHT KIDNEY
Relative renal function (%)	51.0	49.0
Pre-diuretic NORA	1.62	0.36
Post-diuretic NORA	0.28	0.10

On the hydronephrotic left kidney, a pre-diuretic NORA of 1.62 (i.e. greater than 1) was compatible with the visualized pelvicalyceal tracer stasis. After furosemide was given, the NORA declined to 0.28, denoting significant tracer clearance. The pre- and post-diuretic NORA values on the right were both below 1, which was expected in a normal kidney.

It was thus concluded that while there was moderate to severe left-sided pelvicalyceal tracer retention, both the visualized good response to furosemide challenge and the calculated NORA post-diuretic attest to the absence of significant mechanical obstruction. No surgical intervention was instituted; surveillance sonography was performed multiple times over the following months, with stable findings.

CASE 2

Two weeks after the first case, our department received a 7-week-old male with congenital hydronephrosis of the left kidney for diuretic-augmented renal imaging, also to evaluate for ureteropelvic junction obstruction. Dynamic imaging of both kidneys was performed in the posterior view for 20 minutes after injection of 25.9 MBq of Tc-99m MAG3. Sequential imaging was again done after injection of 6 mg furosemide. Gravity-assisted post-void image was obtained afterwards.

The right kidney showed adequate perfusion, good cortical tracer extraction, prompt excretion, and complete tracer washout post-diuretic (Figures 4 and 5). In contrast, the hydronephrotic left kidney exhibited impaired perfusion and function, with tracer retention in the pelvicalyces that increased in severity after diuretic administration. The time-activity curve (Figure 6) showed an upsloping curve which persistently plateaued, even during the post-diuretic study.

Kidney counts were subsequently extracted and NORA values calculated, as in the first case (Tables 3 and 4). The right kidney NORA values were essentially unremarkable. The left kidney NORA, while showing some decline post-diuretic, remained greater than 1.

It was thus concluded that, apart from the left kidney having reduced perfusion and function, there was significant mechanical obstruction at the level of the ureteropelvic junction. The latter finding is supported visually by severe pelvicalyceal tracer retention without response to furosemide challenge, as well as by the time-activity curve and the post-diuretic NORA.

DISCUSSION

A discussion on normalized residual activity would be insufficient without a prologue on semiquantitative indices in measuring renal drainage, particularly after furosemide challenge. Perhaps the most well-known parameter is clearance half-time (T½), the time it takes for renal activity to fall to 50% of its maximum value. A T½ less than 10 minutes is compatible with absence of mechanical obstruction, while a T½ greater than 20 minutes is indicative of obstructive uropathy [5]. However, data is lacking in the pediatric population that

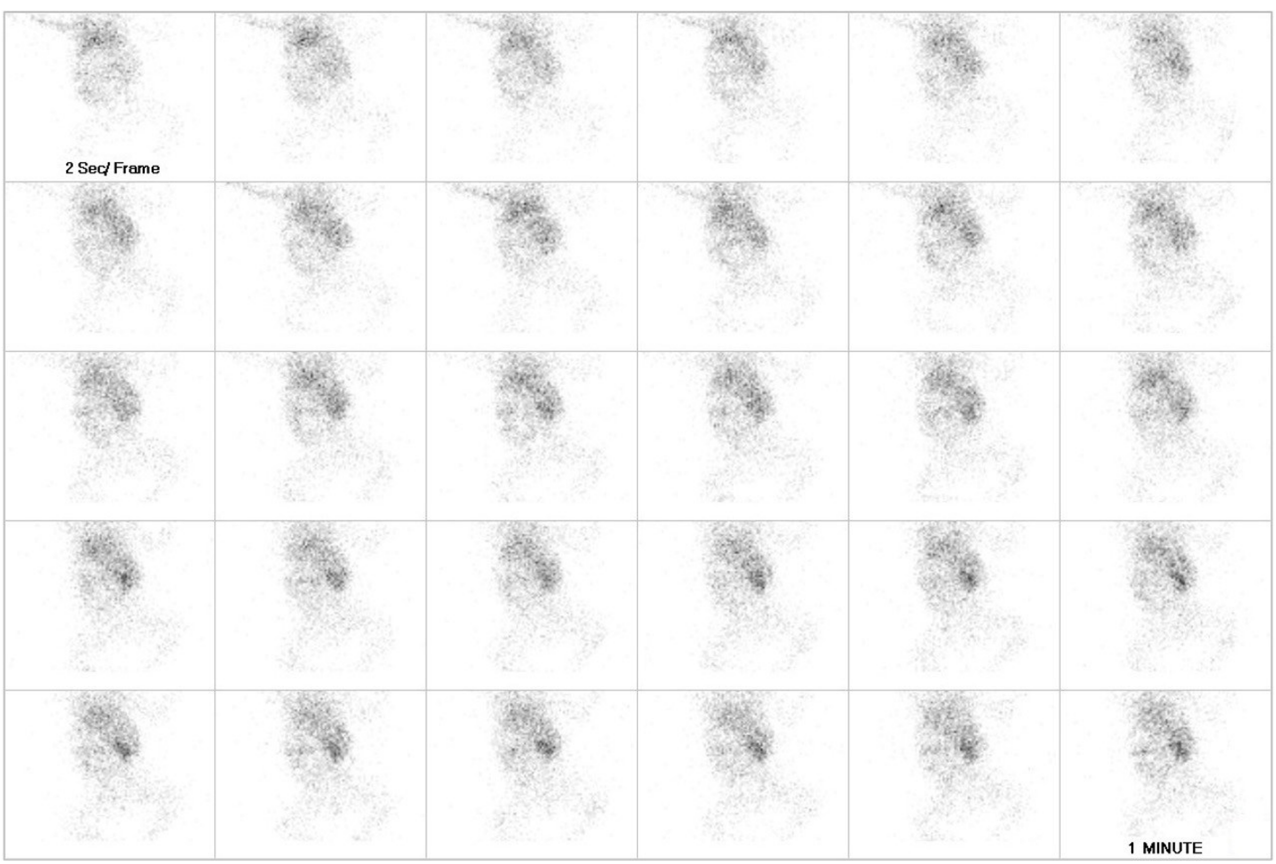


FIGURE 4. Perfusion images of the 7-week-old patient

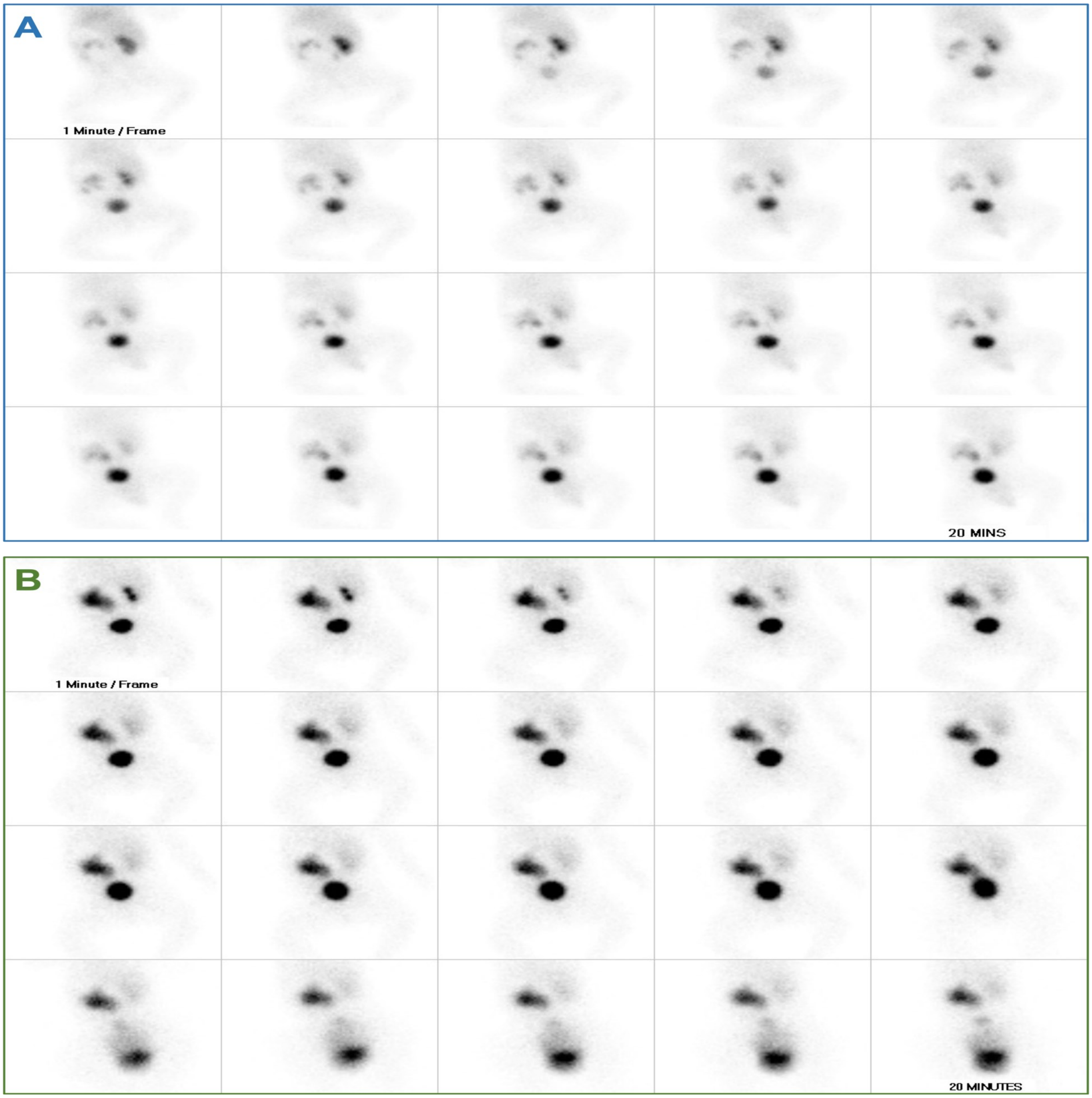


FIGURE 5. 20-minute pre-diuretic (A) and post-diuretic (B) dynamic images of the 7-week-old patient. Acquisition was paused 15 minutes post-diuretic due to involuntary patient voiding, hence the discordant appearance of the 16-20 minute dynamic images.

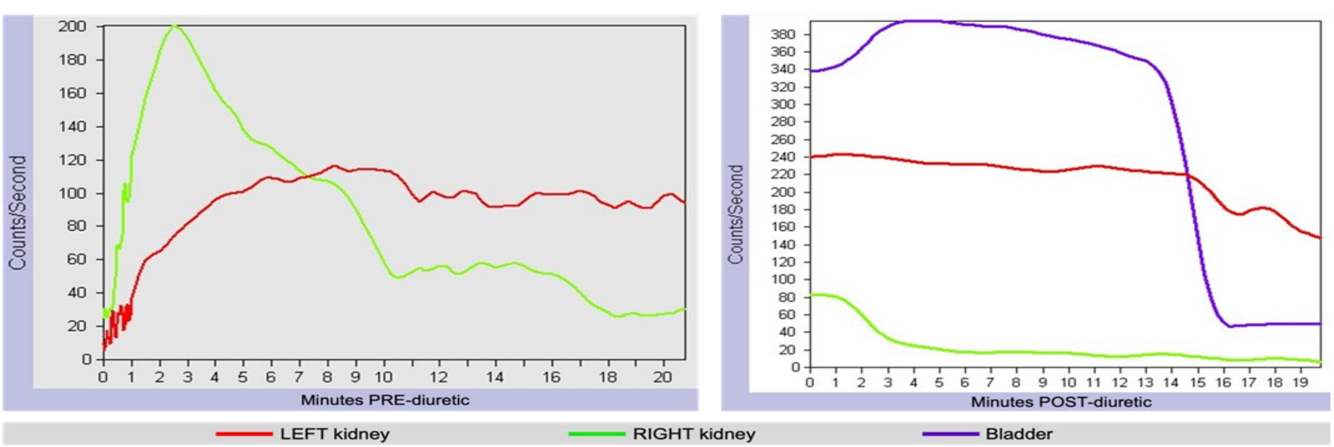


FIGURE 6. Pre- and post-diuretic time-activity curves of the 7-week-old patient. Acquisition was paused 15 minutes post-diuretic due to involuntary patient voiding, hence the abrupt downslope of the bladder curve at around this time.

will allow the interpretation of impaired T½ as obstruction [6]. Another such parameter is output efficiency (OE), defined as the amount of tracer that has left the kidney in proportion to that taken up from the blood. Among children, an OE of less than 89% in normal kidneys and less than 79% in hydronephrotic kidneys is said to be an independent predictor of obstruction, with a diagnostic accuracy of 89% [7]. However, calculation of OE requires specialized software that is not supported by many of the gamma camera vendors.

A formal introduction of NORA as an index of renal emptying was provided by Piepsz et al., showing good correlation between post-diuretic NORA and OE [8]. They defined two parameters that had to be standardized to ensure the robustness of NORA:

- *Background correction.* It was determined that background-corrected NORA was lower than non-background-corrected NORA, regardless of the shape of the background ROI (perirenal or subrenal). This was addressed in the pediatric diuretic scan guidelines by defining the use of a perirenal configuration in the placement of the background ROI.
- *Error of estimating 2-minute renal activity*. A significant delay between starting the acquisition and injecting the tracer would yield a false representative image of maximum tracer accumulation in the renal parenchyma. The seminal paper showed that a delay of 20 seconds led to a systematic 10-15% underestimation of NORA. In our institution, technologists are trained to perform bolus injection within 2-3 seconds of starting image acquisition.

The two cases presented had several common characteristics: both involved infants with left-sided congenital hydronephrosis and were being evaluated for obstructive uropathy. The absence of significant obstruction in the first case was reflected by the NORA value declining to less than 1 after the diuretic was administered. In contrast, the NORA value in the second case remained above 1 post-diuretic in spite of exhibiting some degree of decline, which, concordant with imaging findings, is indicative of significant mechanical obstruction. Apart from the differences in NORA values, the fact that perfusion and function has diminished in the second case is a surrogate indicator of the chronicity of the obstruction, something not seen in the first case.

It can be argued that an adequate interpretation of these cases can be made based solely on the images and renograms. Semiquantitative indices, particularly NORA in this population, provide information that would support what is visually deduced from the acquired images. These parameters may be particularly helpful in cases that are qualitatively equivocal for the presence of obstruction.

While the utility of NORA in infants and children suspected of obstructive uropathy is well-documented, the same cannot be said in the adult population. The latest guidelines on diuretic renal scintigraphy for adults, also released in 2018, acknowledge the potential of semiquantitative indices such as NORA and OE in decreasing the number of false-positive or indeterminate diuretic renal scans. However, it also mentions explicitly that further studies are needed to confirm its utility in the non-pediatric demographic [9].

Pediatric diuretic imaging guidelines endorse the calculation and reporting of normalized residual activity. The case illustrations attest to both the reproducibility of image processing for NORA determination and the utility of NORA as a semiquantitative index of renal emptying. Not all local nuclear medicine institutions are adequately equipped to perform the necessary image processing for every pediatric renal scan patient, and not all pediatric diuretic renal scans would need to be processed as such. Therefore, further studies are suggested to ascertain the overall benefit of NORA calculation in a larger sample of Filipino cases of pediatric hydronephrosis, as well as in those scans where imaging findings are indeterminate for obstructive uropathy.

REFERENCES

1. Majd M, Bar-Sever Z, Santos AI, and De Palma D. The SNMMI and EANM procedural guidelines for diuresis renography in infants and children. J Nucl Med. 2018;59 (10):1636-1640. doi: 10.2967/jnumed.118.215921. PMID: 30275286. PMCID: PMC6167528. American Cancer Society. (2020). Cancer Statistics Center. Retrieved July 26, 2020, from https://cancerstatisticscenter.cancer.org/
2. Taylor AT. Radionuclides in nephrourology, part 1: radiopharmaceuticals, quality control, and quantitative indices. J Nucl Med. 2014;55(4):608-615. doi: 10.2967/ jnumed.113.133447. PMID: 24549283. PMCID: PMC4061739.
3. Shulkin BL, Mandell GA, Cooper JA, Leonard JC, Majd M, Parisi MT, et al. Procedure guideline for diuretic renography in children 3.0. J Nucl Med Technol. 2008;36

(3):162-168. doi: 10.2967/jnmt.108.056622. PMID: 18765635.

4. Lassman M and Treves ST. Pediatric radiopharmaceutical administration: harmonization of the 2007 EANM paediatric dosage card (version 1.5.2008) and the 2010 North American consensus guidelines. Eur J Nucl Med Mol Imaging. 2014;41:1036-1041. doi: 10.1007/s00259-014-2731-9. PMID: 24599377.
5. Taylor AT. Radionuclides in nephrourology, part 2: pitfalls and diagnostic applications. J Nucl Med. 2014;55(5):786-798. doi: 10.2967/jnumed.113.133454. PMID: 24591488. PMCID: PMC4451959.
6. Gordon I, Piepsz A, and Sixt R. Guidelines for standard and diuretic renogram in children. Eur J Nucl Med Mol Imaging. 2011;38(6):1175-1188. doi: 10.1007/s00259-011-1811-3. PMID: 21503762.
7. Saunders CAB, Choong KKL, Larcos G, Farlow D, and Gruenewald SM. Assessment of pediatric hydronephrosis using output efficiency. J Nucl Med. 1997;38(9):1483-1486. PMID: 9293814.
8. Piepsz A, Kuyvenhoven JD, Tondeur M, and Ham H. Normalized residual activity: usual values and robustness of the method. J Nucl Med. 2002;43(1):33-38. PMID: 11801700.
9. Taylor AT, Brandon DC, de Palma D, Blaufox MD, Durand E, Erbas B, et al. SNMMI procedure standard/EANM practice guideline for diuretic renal scintigraphy in adults with suspected upper urinary tract obstruction 1.0. Semin Nucl Med. 2018;48(4):377-390. doi: 10.1053/ j.semnuclmed.2018.02.010. PMID: 29852947. PMCID: PMC6020824.