INTRODUCTION

Radionuclide renography has been used for at least four decades in pediatric urology and nephrology to evaluate differential renal function and kidney excretion. The most common indications in this age group are various uropathies, preceding indirect radionuclide cystography (IRC), systemic hypertension, renal trauma and follow up of renal transplantation. In case of the upper urinary tract suspected obstruction, the standard renography is complemented by a diuretic renogram. A traditional diuresis renogram consists of 20min dynamic study followed by the administration of furosemide and an additional 20min study later. In order to shorten the acquisition time during which children have to remain still and to avoid multiple puncture of veins, a renogram with simultaneous injection of tracer and furosemide (F+0) has been introduced. Meanwhile, it was proposed that this protocol can be used to evaluate patients for renovascular hypertension and diffuse parenchymal disease.

In the departments where the Rutland-Patlak plot is used for calculation of differential renal function (DRF), the furosemide is given two minutes after tracer injection (F+2), since the very quick transit of tracer through the kidney due to the effect of furosemide might invalidate the fitting process for estimation of DRF.
Injecting furosemide at the beginning of the study (F+2) affects the shape of the curve and changes the values of parameters that are used for characterization of transit through the kidneys. This can cause difficulties in the interpretation and reporting of diuretic (F+2) renogram, particularly for the less experienced physicians.

The objectives of the present work were: a) to compare, in children, the pattern of excretion for technetium-99m mercapto-acetyltriglycine ($^{99m}$TcMAG$_3$) of the F+20 renogram and the F+2 renogram and b) to determine normal values of the parameters of renal washout for both standard renogram and F+2 diuretic renogram.

**PATIENTS AND METHODS**

A sample of patients for the study was drawn from the population of children and infants who were referred from the Pediatric urology department because of the unilateral urological or renal disorder, predominantly hydronephrosis (HN) on one side.

They had undergone Tc-99mMAG$_3$ renography with furosemide stimulation. All selected children had normal urinary analysis, were in good health and asymptomatic. They had completely normal kidney contralateral to affected kidney. The criteria for classifying a kidney as normal were: absence of any structural anomaly on ultrasound examination, and/or on the $^{99m}$Tc dimercapto-succinic acid ($^{99m}$Tc DMSA) scan, as well as complete elimination of the tracer from the kidney during renogram, observed on sequential images and represented by the curve shape. The children in whom the affected kidney was nonfunctional were excluded.

On the basis of these criteria, 77 children were selected. Among them, 33 underwent the standard renogram, followed by the injection of furosemide at 20min (F+20), (Group 1) and 44 F+2 diuresis renogram, obtained by injecting furosemide after 2min, (Group 2). There were 41 boys and 36 girls, with age range: 2-120 months. In total, 77 kidneys were analyzed.

### TABLE 1

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n-number of single kidneys, $T_{max}$ time to peak height, $T_{1/2}$ time to half maximum activity, NORA20 normalized residual activity at 20 minutes, OE20 output efficiency at 20 minutes, RA residual activity, EI elimination index, MTT whole kidney mean transit time, p* significance level from comparison of group 1 and group 2.
DATA ACQUISITION

The diuretic renography protocol comprised oral hydration 60min prior to the study. The infants received an additional bottle or breast feed, while children drank liberally 250-500mL of water or juice. Intravenous hydration was not performed. There was no urinary bladder catheterization. The toilet trained children voided immediately prior to the renogram.

Posterior imaging with the child in the supine position was performed and images were acquired with a large field of view γ camera (Siemens Orbiter 7500, Siemens, Germany) and a low energy all purpose collimator attached to a p-computer. A 128x128 matrix size was applied without any zoom factor. To keep the child still under the camera, we used the Velcro straps on either side. The heart and the kidneys were included in the field of view. The dose of 99mTc MAG3 was adjusted for body weight, with a minimum of 19MBq and a maximum of 70MBq, according to the published Guidelines for renography in children[3,7]. The computer started when the activity injected entered the field of view of the γ camera. In children in Group 1 who underwent the F+20 renogram, 240 images of 10sec duration (40min) were acquired. In Group 2 for the F+2 renogram a 22min acquisition protocol with 132 images of 10sec each was applied and furosemide was administered 2min after the start of acquisition. The dose of furosemide was 1mg/kg.
in infants and 0.5mg/kg in children above the age of one year, with a maximum dose of 20mg. A post-void static image of 1min duration was acquired 60-70min after the tracer injection in both groups.

The study protocol was approved by the Ethics Committee, and a written informed consent was obtained from the parents of all participants.

PROCESSING

For data processing, "The International Atomic Energy Agency (IAEA) Software Package for the Analysis of Scintigraphic Renal Dynamic Studies" was used.

Before analysis, each study was checked for possible uneasiness and movements of the child and an automatic motion correction was performed if necessary. Regions of interest (ROI) of the left ventricle and both kidneys were drawn. The cardiac ROI was mandatory for deconvolution analysis of the renogram and for the Rutland-Patlak (RP) analysis. After the kidney ROI was accepted, the program automatically defined the ROI of peri-renal background. We determined DRF by using both integral and the RP plot methods.

From the background corrected time-activity curves the following parameters were calculated: the time to maximum activity (T_{max}), time to half maximum (T_{1/2}), output efficiency at 20min (OE 20), the residual kidney counts at 20min normalized to the 1-2min counts (normalized residual activity, NORA20), the residual kidney counts at 20min normalized to the maximum counts (residual activity, RA), the ratio of the kidney activity at 3min to that at 20min (elimination index; EI) and whole kidney mean transit time (MTT).

STATISTICAL ANALYSIS

The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to check for Gaussian distribution for all parameters. The mean, standard deviation (SD), median, minimum, maximum, 5th- and 95th percentiles were used to describe normal values. The Student's unpaired t-test and Mann-Whitney U-test were used to compare the values.
between the left and right kidneys, as well as between two renogram protocols. The correspondence between OE 20 and NORA20 was assessed by Pearson correlation coefficient and linear regression analysis.

The statistical significance was set below 0.05 level. The SPSS ver. 21 and MedCalc software packages were used.

RESULTS

In Group 1, 33 kidneys were tested, 14 left and 19 right. Thirty kidneys out of 33 had normal DRF (45% - 55%). Only three kidneys had DRF above normal (62%, 69% and 73%, respectively). Evaluation of the differences between the left and right kidneys showed no significant difference for all measured parameters (p>0.05). For that reason, the left and right kidneys were evaluated together. In Group 2, 44 kidneys were evaluated, 17 left and 27 right. Thirty nine kidneys had normal DRF, in two kidneys DRF was slightly under normal (42% and 43%, respectively), and in three kidneys DRF was above normal (64%, 71% and 75%, respectively). As for the Group 1, no significant difference between left and right kidneys was shown (p>0.05) and the kidneys were evaluated together.

The results of statistical analysis for two different renography protocols are shown in Table 1 and Figure 1. The mean, standard deviation (SD), median, minimum, maximum 5th and 95th percentile are given for Tmax, T1/2, NORA20, OE20, RA, EI, and MTT. As expected, the values for NORA20, RA and MTT were low, whereas the OE20 and EI were high for both protocols of diuretic renography.

A significant difference between the two protocols of the diuretic renogram was obtained for the values of T1/2, OE20, NORA20, RA and EI, and MTT (P<0.05). Only for the Tmax no significant difference was observed (P>0.05).

The linear regression analysis with OE20 as the input variable and NORA20 as the dependent variable was significant (P<0.01). The goodness of linear fit was high (R² = 0.82 and R² = 0.84, for Groups 1 and 2, respectively; Fig. 2).

DISCUSSION

This study, performed on the population of children, compared the pattern of excretion on standard renogram and on F+2 diuresis renogram. The overall results provide evidence of significantly accelerated washout of tracer from the kidney after early injection of furosemide. During the F+2 protocol of diuresis renography, the normal kidneys showed Tmax <5min, T1/2 <7.5min, NORA 20 <0.4, OE 20 >90%, RA <30% and EI >3.5.

The 99mTc MAG3 has been used as the radiopharmaceutical of choice for the dynamic renal scintigraphy in children. After the introduction of F+0 protocol it was suggested that the quick washout of tracer from the kidney might affect the shape of the curve and change the values of the excretion parameters. The normal values for the F+0 diuresis renogram in children had been previously reported for Tmax, T1/2, NORA and OE

The F+2 diuresis renogram, although uncommon, was used in the present study because the DRF was calculated through two independent methods, the integral and the RP method. When RP method is used, it is recommended to apply F+2 protocol, to avoid the effect of furosemide on the earliest part of the renogram, and to provide more points for curve fitting procedure.

Several semi-quantitative parameters of diuresis renogram were analyzed. We found it useful to report the values not only for more sophisticated indices, but also for simpler ones, because many nuclear medicine departments in our region do not have the facilities for performing more complex renogram analysis.

Tmax and T1/2, are traditional, mostly empirical parameters, but they are readily estimated and recommended in guidelines for reporting diuresis renography. RA and EI are parameters that had been recommended as adjuncts to image interpretation. NORA is also simple, but robust parameter, that provide an estimation of the washout of a kidney, independently from the differential renal function. OE is more accurate parameter which normalizes output to overall kidney function. Mean transit time, calculated by means of deconvolution is theoretically the most accurate indicator of renal transit, although its role in various clinical situations has still to be properly evaluated.

The values of Tmax observed in this study did not differ between the two groups due to the delay of at least two minutes between the injection of tracer and of furosemide. The results closely agreed with previously reported normal values for 99mTc MAG3 obtained in healthy individuals and showed higher values compared to F+0 renogram.

As was expected, among other measured parameters, T1/2, NORA 20, RA, and MTT showed significantly lower values, while OE 20 and EI were significantly higher in the case of early diuretic stimulation compared with standard renogram. Comparing the results of present study for F+2 protocol with previously reported normal ranges for T1/2, NORA 20 and OE 20 F+0 renogram, almost identical values were observed.

Residual activity (RA) and elimination index (EI) both represent urine flow rate and in most cases the value of the first one is the inverse value of the second one, so either one parameter can be used as an aid to visual analysis of the renogram. The values observed in our study completely agreed with the literature. The proposed normal values of EI were ≥3, which was in agreement with the values of ≥3.6 and of ≥3.1 which we obtained from the F+2 renogram and standard renogram, respectively.

The normal ranges for MTT are not widely reported in the literature. We found that the normal value of MTT for adults was 2.9±0.5 min. The results obtained in the present study were lower than expected, which requires further clarification.
The linear regression analysis indicated a close correspondence between OE 20 and NORA20. This result supported the statement that the clinical information on kidney excretion provided by both OE 20 and NORA20 is identical, and that NORA, being easier to programme, could replace OE in the evaluation of renal drainage.

**STUDY LIMITATIONS**

The main limitation of this study refers to limited number of children that were included in the analysis, which is due to short period of time during which the study was conducted, because the IAEA software has been recently implemented in our department. We hope that the upcoming implementation of software in nuclear medicine centers in our country will enable the exchange of results between the departments. That would create the opportunity to conduct multi-center studies on a large number of patients, which will improve the accuracy of further analysis.

**CONCLUSION**

We evaluated several semi-quantitative parameters of $^{99m}$Tc MAG$_3$ diureis renogram performed according to the standard F+20 protocol and F+2 protocol. The obtained normal ranges for F+2 diureis renogram indicated significantly accelerated transit through renal parenchyma and collecting system, when compared with with standard (F+20) renogram. The values for T$_{1/2}$, NORA 20, OE 20, RA, EI, and MTT were almost identical to those previously reported reference values for the F+0 diureis renogram, whereas the values for Tmax were in accordance with the reference values for standard renogram. Applying these values to the interpretation of $^{99m}$Tc MAG$_3$ diureis renogram would help nuclear medicine physicians to distinguish the normal from the pathological findings. The semi-quantitative parameters facilitate the comparison between studies during follow up and contribute to better management of children with antenatal hydronephrosis.

**SUMMARY**

**POREDJENJE DVA PROTOKOLA DIUREZNE RADIONUKLIDNE RENOGRAFIJE KOD DECE: RENOGRAM SA FUROSEMIDOM U 20. MINUTU U ODNASU NA RENOGRAM SA FUROSEMIDOM POSLE 2 MINUTA**

**Cilj rada.** Ciljevi našeg ispitivanja, radjenog u pacijentama sa unilateralnom, prenatálno dijagnostikovanom hidronefrozom (HN) i kontralateralnim normalnim bubregom. Ispitanci su podeljeni u dve grupe: grupu 1, od 33 deteta kod kojih je radjena F+20 diurezna renografija, i grupu 2, od 44 dece sa F+2 diureznom renografijom. Ispitivani su samo normalni bubrez, kontralateralni u odnosu na bubreg sa HN. Ukupno je analizirano 77 bubrega. Za obradu renografije korišćen je software Medjunarodne aгенције za atomsku energiju (International Atomic Energy Agency, IAEA). Izračunavani su sledeći parametri diuretske renografije: vreme dostizanja maksimalne aktivnosti ($T_{\text{max}}$), vreme poluvelimina u odnosu na normalnu aktivnost u 20. minuti (NORA20), efikasnost eliminacije posle 20 minuta (OE20), normalna aktivnost (RA), indeks eliminacije (EI) i srednje vreme transzita kroz bubreg (MTT). U proceni rezultatula istraživanja korišćene su metode deskriptivne i analitičke statistike.

**Rezultati.** Prosečan uzrast dece bio je 26 meseci (opseg: 2-120 meseci). Vrednosti merenih parametara u grupi 1 su bile: $T_{\text{max}}$: 3.3±0.6min; T$_{1/2}$: 5.7±1.4min; NORA 20: 0.31±0.08; OE 20: 93±1.5%; RA: 22±2%; EI: 4.6±1.0; MTT:2.1±0.3min. U uslovima rane diuratske stimulacije transzit kroz sabirni sistem se značajno ubrzava, u porodjenju sa standardnom renografijom (P<0.05). Vrednosti u grupi 2 su bile: $T_{\text{max}}$: 3.2±0.6min; T$_{1/2}$: 3.7±1.4min; NORA20: 0.25±0.06; OE20: 95±1.5%; RA: 18±5%; EI: 5.7±1.9; MTT: 1.9±0.4min. Analizom linearne regresije je utvrđena značajna linearna povezanost izmedju OE 20 i NORA20 (R$^2=0.84; P<0.01$).

**Zaključak.** Normalni opsezi vrednosti parametara diuretskog renograma kod ispitanika dečijeg uzrasta su određeni za dva protokola diurezne renografije (F+20 i F+2). Primena ovih vrednosti omogućava tačnije definisanje fiziološkog transzita kroz parenhlim i sabirni sistem bubrega, što doprinosi preciznom razlikovanju normalnih u odnosu na opstruktnive bubrego, olakšava praćenje stanja bubrega sa HN i donošenje odluke o konzervativnom ili hirurškom lečenju.

**Ključne reči:** deca, Tc-99m MAG$_3$, diurezna renografija, efikasnost eliminacije, normalizovana rezidualna aktivnost, normalne vrednosti

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The authors declare that they have no conflicts of interest.