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Diuresis renal scintigraphy "F-0" in diagnosing of upper urinary tract obstruction in children: the clinical significance

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Abstract

BACKGROUND: The aim of this study was to assess the clinical relevance of diuresis renal scintigraphy after simultaneously administered radiopharmaceutical and diuretic (DRS "F-0") in diagnosing obstruction of upper urinary tract in children with previously documented hydronephrosis and ureterohydronephrosis, analyzing the value of qualitative and quantitative scintigraphy parameters.

MATERIAL AND METHODS: This retrospective study enrolled 82 children (30 girls and 52 boys aged between 2 months and 16 years; mean 5.8 ± 4.5 years) with previously documented hydronephrosis or ureterohydronephrosis (42 left-sided, 28 right-sided and 12 bilateral). DRS "F-0" was started after intravenous administration of diethylene-triamine- pentaacetic acid (DTPA) mixed with furosemide. Results of DRS "F-0" were analyzed qualitatively (visual analysis of scintigrams and renography curves) and quantitatively (time to reach maximum of the kidney curve-T max, washout of the tracer-WO, the furosemide clearance half-time (F/2) and individual kidney function — IKF) and compared with the final diagnoses obtained in 37 children (42 nephroureteric units — NU) after surgery, in 41 children (48 NU) during the medical follow-up lasting at least 6 months, and in 4 children (4 NU) using invasive diagnostic procedures. Diagnostic criteria for obstructed NU (kidney with corresponding ureter) considered presence of pathological at least two of five scintigraphy variables characterized as a sign of obstruction.

RESULTS: Forty true positive and 37 true negative results were detected using diagnostic criteria for obstructed and normal NU by means of DRS „F-0". DRS „F-0" failed to detect obstruction in 5 children with a total of 6 obstructed NU, while the results were marked as false positive in 9 children (11 NU). Qualitative scintigraphy analysis was found to be the most sensitive (91%) and accurate predictor (85%) in differentiating obstruction from non-obstructive renal unit. High sensitivity in predicting obstruction was also found for both washout of the radiopharmaceutical (87%) and for furosemide clearance half time (85%). Overall sensitivity of DRS "F-0" using proposed diagnostic criteria in differentiating obstruction was 87%, specificity 77% and accuracy 82%. However, DRS "F-0" has been shown to be more sensitive (90%) in children with UPJ and UVJ obstruction concerning children in whom obstruction was caused by other urinary tract diseases.

CONCLUSION: This study showed DRS "F-0" as a sensitive and reliable method in diagnosing children with obstructions of the upper urinary tract. The great advantage of the protocol DRS „F-0" over other diuresis renography protocol modalities is due to the shorter time of the acquisition by half, and the avoidance of additional diuretic application. However, conventional quantitation of diuresis renogram did not improve the sensitivity and specificity with respect to the qualitative analysis of scintigrams and renography curves.

Key words: diuresis renal scintigraphy, children, furosemide

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Introduction

Hydronephrosis is reported in 50% of all congenital malformations [1]. It is now well established that hydronephrosis is not necessarily equivalent to obstruction. In a practical sense, obstruction is defined as functional or anatomic disorders of urine flow anywhere from the renal pelvis to the urethra that, if left untreated, induces symptoms or renal damage. Hydronephrosis and uretero-hydronephrosis are often incidentally detected during sonography. However, like other radiological imaging procedures, sonography can ensure only the actual morphological situation in a very restrictive moment of the investigation. Urodynamic effectiveness of hydronephrosis as a measure of the washout kinetic of the fluid excreted by the kidneys becomes imperative, when noticed.

The pressure flow study, or Whitaker test, remains the gold standard for the determination of obstruction [2]. This procedure is generally considered too invasive for routine use, because it requires puncture of the renal pelvis and catheterization of the distal ureter to ensure fluid under pressure and to measure pelviureteral flow rates. In addition to being invasive, this method requires general anaesthesia in children, specific urodynamic equipment and experienced physicians for interpretation.

Since its introduction by O'Reilly et al [3], diuresis renal scintigraphy (DRS) has become a widely accepted imaging modality that can differentiate obstruction of the upper urinary tract in a non-invasive manner. Although this method is performed differently at various medical centres, the reliability of DRS findings in distinguishing obstruction from non-obstructive dilatation of the upper urinary tract has been proven many times. Historically, the practice of DRS has suffered from a lack of standardized protocols. Although several consensus guidelines published since 1991 reached an agreement in broad areas, they did not resolve the problems because the consensus papers themselves did not agree on important issues, including preparation of the patient before the study, radiopharmaceutical choice, acquisition protocol and interpretation criteria [4–8]. The most common variation between the protocols included the timing of the diuretic injection and the interpretation criteria for preparing the final DRS report. The protocol, which proposes application of diuretic and radiopharmaceutical simultaneously (DRS "F-0"), promises the further improvement in diagnosing obstruction of upper urinary tract, especially in children. The important advantage of protocol DRS „F-0" over the other protocols is shortening the procedure by half and omitting the diuretic injection. The aim of this study was to assess the clinical relevance of diuresis renal scintigraphy after simultaneously administrated radiopharmaceutical and diuretic in diagnosing obstruction of upper urinary tract in children with previously documented hydronephrosis and ureterohydronephrosis and analyzing the value of qualitative and quantitative scintigraphy parameters.

Material and methods

Study group

During the past 36 months, 82 children (30 girls and 52 boys aged between 2 months and 16 years; mean 5.8 $\pm$ 4.5 years) with previously documented hydronephrosis or ureterohydronephrosis were examined by means of DRS "F-0", and were subsequently enrolled into this retrospective study. There were no specific selection criteria for the acceptance, and all the children with echosonography-diagnosed hydronephrosis or ureterohydronephrosis were included in the prospective investigation, and were subjected to DRS „F-0". There were 42 left-sided, 28 right-sided and 12 bilateral hydronephrosis or ureterohydronephrosis. All children have had two kidneys except one with neurogenic bladder and solitary kidney. The serum creatinine values were within the normal range (from 45 μmol/L to 113 μmol/L) in 79 patients. Borderline high creatinine levels of 114 μmol/L and 117 μmol/L were detected in two children, while the child with solitary kidney and advanced renal failure had a high serum creatinine value of 300 μmol/L. The results of DRS "F-0" were compared with the final diagnoses which were established in 37 children (42 nephroureteric units) after surgery, in 41 children after the medical follow-up lasting at least 6 months (48 nephroureteric units), and in 4 children (4 nephroureteric units) using invasive diagnostic procedures (cystoscopy with retrograde pyelography, ante-grade pyelography, or a Whitaker ante-grade perfusion test).

Patient preparation and acquisition protocol

Children were orally hydrated before commencement of the study, for one-hour prior, taking the water or juice in a total of 10–20 ml/kg b.w. Infants were breast-feeding before the study and the quantity of the milk in this situation could not be estimated. Children have not been catheterized before the study except one with neurogenic bladder who has been managed using clean intermittent catheterization. Patients with volitional bladder control were asked to void immediately before the study, while infants were examined just after changing the wet diaper.

Diuresis renal scintigraphy was done using a Siemens single-head gamma camera equipped with a low energy all-purpose parallel hole collimator. Studies were done in the back projection of the sitting child. Infants were positioned in the supine projection lying on the face of the gamma camera. Acquisition was performed collecting 20s frames over 20 min in a 64 $\times$ 64 computer matrix. Diuresis renal scintigraphy was started after intravenous administration of the weight-adjusted dose (minimum 20 MBq) of diethylene-triamine-pentaacetic acid (DTPA) [9] mixed with furosemide in a dose of 1 mg/kg b.w. (maximum 60 mg in renal failure) through indwelling venous catheter. Post-micturating one-minute bladder static scintigrams were performed in all children with unilateral stasis. Indirect radionuclide cystography [10] was performed in all children who developed volitional bladder control and were noticed to have bilateral stasis.

Interpretation criteria

Results of DRS "F-0" were analyzed qualitatively and quantitatively. Qualitative interpretation was based both on the visual analysis of sequential scintigrams and on the type of the renography curves. Significant sign of obstruction was considered in units with progressive accumulation of the radiopharmaceutical either in the renal pelvicaliceal system or in both renal pelvis and corresponding ureter with an accumulation renography curve or when much delayed radiotracer excretion was observed. Obstruction was also diagnosed if the kidneys have not been visualized on sequential scintigrams in the presence of hydronephrosis or ureterohydronephrosis on echosonographic examination. Non obstructed unit was considered if vi-

sual analysis showed good radiopharmaceutical excretion with normal or slightly delayed excretion noticed on the renography curve.

For each study, quantitative variables were determined from the background subtracted time activity curves obtained from the region of the whole kidney as follows:

— time to reach the maximum of the kidney curve (T max) expressed in min;
— washout (WO) as the percentage of the radiopharmaceutical excreted by the kidneys after forced diuresis achievment was calculated by comparing the minimal activity at the end of the study (A min) and peak activity (A max) using the following equation:

$$WO\ (\%) = (1\text{-}A\ min/A\ max) \times 100$$

— the furosemide clearance half-time (F/2) was generated from the exponential fit of the maximal slope of the descending component of the renogram curve;
— individual kidney function (IKF) was calculated from the net counts accumulated by each kidney over 60–100 s.

Diagnostic criteria for obstructed nephro-ureteric unit (kidney with corresponding ureter) considered presence of pathological at least two of five scintigraphy variables characterized as a sign of obstruction.

Statistical analysis

Parameters were presented as individual values as well as mean ± standard deviation (SD). For the quantitative variables T max, WO and F/2, cut-off values were determined with respect to the means ± 2 SD.

Results

Table 1 presents the values of quantitative scintigraphy parameters obtained using DTPA DRS "F-0" for 69 contralateral kidneys of children with unilateral hydronephrosis or ureterohydronephrosis. Mean values ± 2 SD for the analyzed parameters that have been determined from the renography curves in normal kidneys have been considered as the normal values. Discriminated values for quantitative variables characterized as a signs of obstruction were determined using the mean value for each variable either plus (T max and F/2) or minus (WO and IKF) 2SD. An exception was made for IKF, for which the discriminated value was considered at least 45% [11].

The presence of obstruction was considered if at least two of five analyzed DRS "F-0" variables suggested obstruction. Table 2 shows the comparison of diuresis renography findings and final diagnoses. Groups of children with UPJ and UVJ stenosis and those in whom obstruction was caused by other diseases of the urinary tract were analyzed separately. Regarding the final diagnoses, 40 true positive and 37 true negative results were detected using diagnostic criteria for obstructed and normal nephro-ureteric units by means of qualitative and quantitative analysis of DRS „F-0". Figure 1 depicts true positive findings in children with left-sided obstruction of ureteropyelic junction (UPJ) (Figure 1A) and ureterovesical junction (UVJ) (Figure 1B).

Diuresis renal scintigraphy „F-0" missed obstruction in 5 children with a total of 6 obstructed nephro-ureteric units (two children with unilateral UPJ stenosis, one child with unilateral UPJ stenosis and consecutive pelvic calculosis, one child with unilateral crossing vessel and one child with bilateral transient hydronephrosis). Figure 2A shows a child with transient hydronephrosis and false negative DRS "F-0" result in the sitting position. The second study, performed in the supine position, proved the obstruction (Figure 2B). All children with false negative DRS"F-0" results were diagnosed to have low-grade obstruction of the kidneys, the function of which was preserved. The results of DRS „F-0" were marked as false positive in 9 children (11 nephro-ureteric units). False positive DRS "F-0" results in two children with preserved renal function were the consequence of marked collecting system dilatation, either post-operatively in one child, or after bilateral extracorporeal shock wave lithothripsy treatment of renal calculus disease in the other one. The child with unilateral caliceal calculi was also diagnosed to have a false positive result on DRS "F-0", due to a huge pelvic dilatation, but without obstruction. The false positive DRS "F-0" report concerning the child with crossing vessels but without obstruction was based on the mild radiopharmaceutical retention into the collecting system and decreased tracer washout below the discriminated value. The results of DRS "F-0" were falsely positive in two children with unilateral severe refluxing megaureters. One of them also developed incipient renal failure. The child with neurogenic bladder dysfunction and a solitary kidney was found to have a false positive DRS „F-0" result. Both severe renal pelvis dilatation and advanced renal failure, which contributed to the false positive DRS "F-0" result were detected despite the fact that bladder catheterization was performed immediately before the study. One child with ultrasound-detected bilateral stasis was falsely marked as having obstruction according to the DRS "F-0" diagnostic criteria, including prolonged T-max and reduced WO. Obstruction was excluded in this child after a six-month medical follow-up. One child, who had slightly

Table 1. Quantitative parameters determined using DRS „F-0" for contralateral kidneys in children with unilateral hydronephrosis and ureterohydronephrosis

Quantitative parameters	Number of kidneys	Minimum	Maximum	Mean ± SD	Cut-off values (Mean ± 2 SD)
T max [min]	69	1.6	5.0	2.5 ± 0.7	> 3.9
WO (%)	69	29	66	45.8 ± 6.2	< 33
F/2 [min]	69	2	14	6.1 ± 2.5	> 11
IKF (%)	69	43	100	55.6 ± 12.2	< 45

DRS "F-0" — diuresis renal scintigraphy "F-0"; T max — time to reach maximal activity; WO — washout of the tracer; F/2 — the furosemide clearance half-time; IKF — individual kidney function; SD — standard deviation

Table 2. Results of DRS „F-0" analysis versus final diagnoses

Final diagnosis	Results of DRS "F-0" *vs.* final diagnoses				Total of NU	Number of children
	TP	TN	FP	FN		
Without obstruction	**–**	**30**	**2**	**–**	**32**	**31**
UPJ and UVJ stenosis:						
UPJ stenosis	25	–	–	2	27	27
UVJ stenosis	1	–	–	–	1	1
Left-sided VUR and right sided UPJ stenosis	1	–	1	–	2	1
Left-sided UPJ stenosis with ipsilateral pelvic calculi	–	–	–	1	1	1
Left-sided UPJ stenosis with ipsilateral VUR	1	–	–	–	1	1
Total	**28**	**–**	**1**	**3**	**32**	**31**
Other diseases						
Caliceal and pelvic calculosis	2	1	1	–	4	3
Post ESWL pelvic dilatation	–	–	2	–	2	1
Postoperative stasis	–	3	1	–	4	2
Crossing vessel	–	–	1	1	2	2
Bladder diverticulum	4	–	–	–	4	2
VUR	–	1	2	–	3	3
Neurogenic bladder with renal failure	–	–	1	–	1	1
Transient hydronephrosis	2	2		2	6	3
Bladder calculi	2	–	–	–	2	1
Ureteral trauma	2	–	–	–	2	2
Total	**12**	**7**	**8**	**3**	**30**	**20**
Total of all	**40**	**37**	**11**	**6**	**94**	**82**

DRS "F-0" — diuresis renal scintigraphy"F-0"; NU — nephro-ureteric unit; UPJ — uretero-pelvic junction; UVJ — uretero-vesical junction; ESWL — extracorporeal shock wave lithotripsy; VUR — vesicoureteral reflux; TP — true positive DRS "F-0" finding; TN — true negative DRS "F-0" finding; FP — false positive DRS "F-0" finding; FN — false negative DRS "F-0" finding

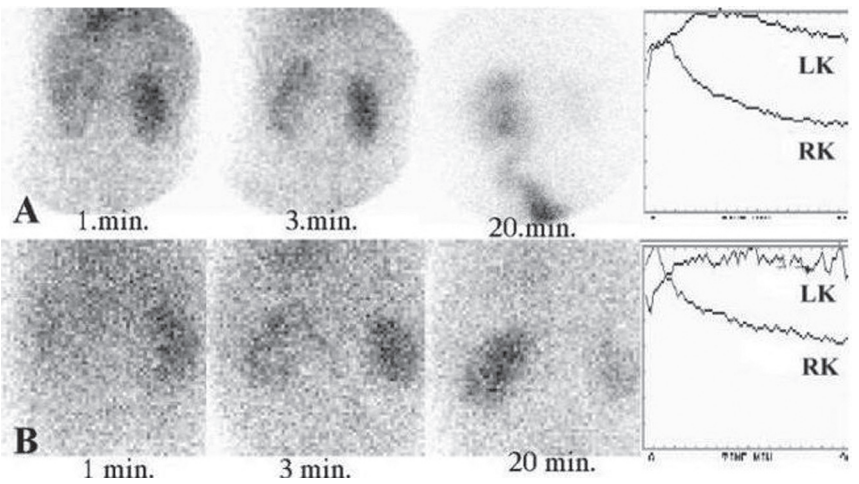

Figure 1. True positive diuresis renal scintigraphy "F-0" findings in children with left-sided obstruction of ureterovesical (A) and left-sided obstruction of ureteropyelic junction (B).

impaired overall renal function with left-sided VUR and right sided UPJ stenosis, was found to have false positive DRS "F-0" result for the left kidney and true positive result for the right. (Figure 3A). This child was detected to have unilateral left- sided VUR using IRNC following DRS "F-0" (Figure 3B) in whom low grade VUR was reconfirmed later using micturating cystourethrography.

Reliability parameters obtained for each analyzed parameter of DRS „F-0" and for the model proposed (at least two out of five parameters) with respect to the final diagnosis are presented in Table 3. Qualitative scintigraphy analysis was found to be the most sensitive (91%) and accurate (85%) predictor in differentiating obstruction from non-obstructive renal unit. High sensitivity in predicting obstruction was also found for both washout of the ra-

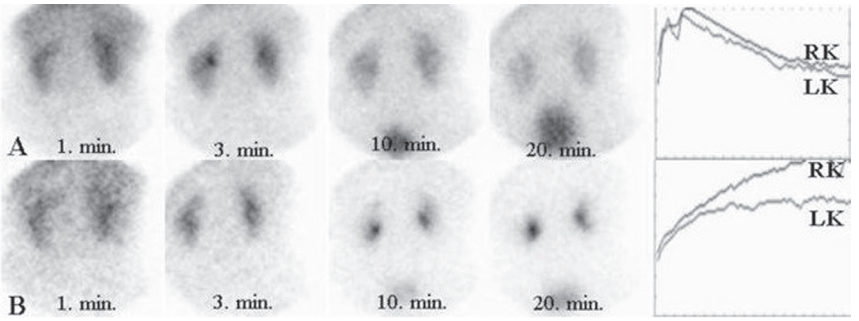

Figure 2. Child with transient hydronephrosis and low grade obstruction (**A**); False negative diuresis renal scintigraphy "F-0" result in the sitting position, and true positive finding of obstruction in the supine position in the same child (**B**).

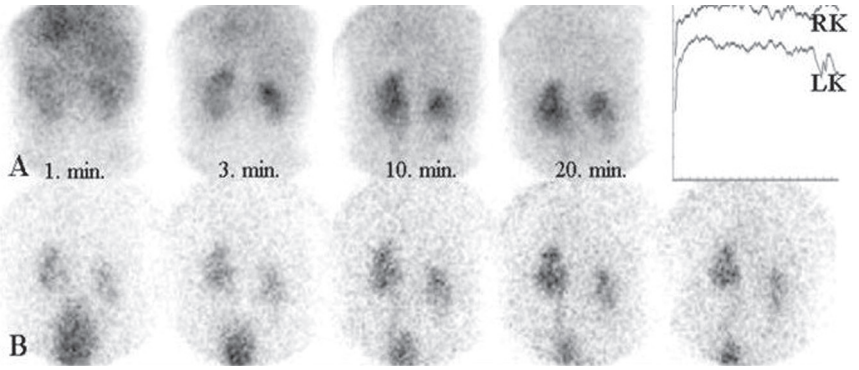

Figure 3. Child with impaired overall renal function and the left-sided vesicoureteral reflux and the right-sided ureteropyelic junction stenosis: false positive result of DRS "F-0" for the left kidney, and true positive result demonstrating obstruction for the right kidney (**A**); Unilateral left-sided reflux detected by means of indirect radionuclide cystography following DRS "F-0" in the same child (**B**).

Table 3. Reliability analysis of DRS "F-0"

Parameters	SE (%)	SP (%)	ACC (%)
T max [min]	83	79	81
WO (%)	87	79	83
F/2 [min]	85	77	81
IKF (%)	43	92	68
Qualitative scintigraphy analysis	91	79	85
Abnormal any 2/5 variables	87	77	82

DRS "F-0" — diuresis renal scintigraphy "F-0"; T max — time to reach maximal activity; WO — washout of the tracer; F/2 — the furosemide clearance half-time; IKF — individual kidney function; SE — sensitivity; SP — specificity; ACC — accuracy

diopharmaceutical (87%) and for furosemide clearance half time (85%). Overall sensitivity of DRS "F-0" using the proposed diagnostic criteria in differentiating obstruction was 87%, specificity 77% and accuracy 82%. However, DRS "F-0" has been shown to be more sensitive (90%) in children with UPJ and UVJ obstruction with respect to children in whom obstruction was caused by other urinary tract diseases. The lowest sensitivity, of 43%, but the highest specificity, of 92%, in diagnosing obstruction was found for the value of individual kidney function.

Discussion

Over the years, a great variety of protocols and techniques for diuretic renography have been suggested. This has produced variability in the interpretative criteria among different nuclear medicine laboratories. Rapid emptying of the collecting system followed by steep a decline of the renography curve is considered specific for non-obstructive dilatation, regardless of diuretic protocol and radiopharmaceutical choice. This was confirmed in our

study, which found the qualitative scintigraphy report as the most sensitive (91%) and accurate (85%) predictor in differentiating obstruction from non-obstructive renal unit.

Quantitative analysis of diuresis scintigrams was introduced as a potentially useful tool to improve reliability of the final report, and to avoid operator dependence in interpretation. The methods used to quantify the transit through the kidney and washout of the tracer vary from simple description to more sophisticated techniques. The time taken to reach maximal curve activity and residual activity at the end of the study are the most commonly used semi-quantitative parameters of diuresis renogram curves [12, 13]. Other reports suggested deconvolution analysis, output efficiency and normalized residual activity [14–18] as the power tools in diuresis scintigraphy interpretation. However, there is no clinical proof that more sophisticated techniques offer additional information.

Variability of protocols and radiopharmaceuticals applied during the diuresis renography offered a wide range of normal values, but still there is no consensus for the cut off values for particular radiopharmaceuticals and protocols. This paper offers normal range values as well as cut off values for DTPA DRS "F-0", determined for healthy kidneys of children with unilateral hydronephrosis, and the cut off values were suggested with respect to the normal means. Furosemide application at the beginning of the study induces a slightly shorter value for the time to reach maximal activity in the majority of normal kidneys, but the wide range of values detected in this study suggests that many factors might have been an influence. The cut off value for T-max of 3.9 min found in our study has been shown as a less sensitive but quite specific parameter in discriminating obstruction from non-obstructive dilatation. The most widely used method for quantifying the response to furosemide is the half-time to tracer clearance, or the time required to achieve 50% clearance of pelvicaliceal activity. The methods for determining this value vary considerably due to the lack of a broadly established standardized approach. The method suggested in this paper, with the construction of a computer-derived exponential best-fit curve of the descending component of the renogram curve, overcomes the potential variability in the length of time required for the onset of the furosemide effect from patient to patient. Our study confirmed furosemide clearance half time as a useful parameter, discriminating obstruction with the cut off value below 11 min. Washout of the tracer after 20 min of study was considered as significant for obstruction if there was more than 67% of maximal activity left. This parameter proved to be sensitive and specific for obstructive pattern. Individual kidney function is a very important parameter in the assessment and management of obstruction. Worsening individual function in hydronephrotic kidneys has been proposed as an indication for surgical intervention and conversely, stable individual function is often the reason for postponing surgery. Our study found individual kidney function as an unreliable parameter to predict the obstruction when analyzed separately, partly due to the relatively high number of bilateral kidney involvements. A lack of standardization resulted in conflicting results about the value of IKF determined from DTPA originated from different methods of determination. Fung and co-workers found kidneys with hydronephrosis to have paradoxically greater differential function than the contralateral normal kidney using DTPA and standard methods for calculation from background subtracted time activity curve between 2–3 min [19]. However, Brookes and Gordon found excellent agreement between IKF in children with unilateral pelvic dilatation, determined from DMSA scans and DTPA if the Rutland-Patlak plot method of calculation was performed [20–22].

The model proposed in this study, based on finding at least two abnormal, out of five, analyzed parameters was found to be sensitive but less specific for obstruction. Even in technically satisfactory DRS studies, false-negative findings occur, and these patients with a negative study in the presence of persistent hydronephrosis or pain may require a follow-up renogram or perhaps a pressure/perfusion study when the clinical situation is still unclear. Thus, with regard to the final diagnosis, this study failed to detect two patients with UPJ stenosis and other with UPJ stenosis and consecutive pyelic calculi and one child with low-grade obstruction due to crossing vessels. These children were subsequently found to have low-grade obstruction and preserved renal function and were operated due to the worsening of the symptoms. Although DRS „F-0" performed in the back projection of the sitting child with transient hydronephrosis did not show the obstruction, further evaluation found obstruction in supine position only. This study demonstrated that the disadvantages of DRS „F-0" could originate from at least two sources, of which the most important are renal function and the degree of collecting system dilatation. In the setting of renal insufficiency, the response of the kidney to furosemide may be impaired and the desired urinary flow rates of 10 ml/minute per kidney may not be achieved [23]. Renal function below 15 ml/min will result in a poor washout effect even in the absence of significant obstruction [24]. In patients who had previously undergone pyeloplasty, or who have a large extra-renal pelvis, dilatation of the renal pelvis may present without obstruction, especially if the patient is imaged in the supine position for the entire study. Slow washout of the tracer may be seen from such a collecting system, resulting in the false positive result of the study. Therefore, images acquired in the upright position should always be performed, either during the post-furosemide part of the study or at completion of the study. Our study has also shown false positive findings in children with huge dilatation of the pelvis postoperatively and in children with impaired renal function. Overall sensitivity for DRS "F-0" and the model proposed in differentiating obstruction was 87%, specificity 77% and accuracy 82%. If the inclusion criteria for the study were more restrictive, the overall sensitivity, specificity and accuracy of DRS "F-0" would be slightly higher. Thus, DRS "F-0" was found to be more sensitive (90%) in children with UPJ and UVJ obstruction with regard to the children in whom obstruction was caused by other urinary tract diseases. The positive predictive value of the test in children with UPS and UVJ stenosis is about 96%, suggesting excellent diagnostic capability in these children. However, the idea was to include all children with previously documented hydronephrosis in order to detect the advantages and shortcomings of the protocol suggested for almost all possible clinical situations that could result in hydronephrosis.

Indirect radionuclide cystography is a suitable non-invasive method based on physiological mechanism of bladder filling being easily performed following renal scintigraphy. This method allows the provision of information about the competence of ureterovesical valve mechanism and bladder function, including functional bladder capacity, residual urine and voiding flow rates [10]. Conside-

ring the possibility that more than one abnormality of the urinary tract may be present at the same time, additional radionuclide investigation after only one radiopharmaceutical application is a very important advantage over other imaging procedures. Results of our study showed the usefulness of indirect radionuclide cystography following DRS in detection of vesicoureteral reflux. This method may also give an outlook of the bladder involvement in upper urinary tract obstruction but the results will be presented elsewhere.

In conclusion, this study showed diuresis renal scintigraphy to be a sensitive and reliable method in diagnosing children with obstruction of the upper urinary tract. The great advantage of the protocol DRS „F-0" over other diuresis renography protocol modalities is its shorter time of acquisition by a half and the avoidance of any additional diuretic application. Less invasiveness and shorter study duration of DRS „F-0" in paediatric population minimize the movements during the acquisition and consequently improve the accuracy of processing the study. However, conventional quantitation of diuresis renogram did not improve the sensitivity and specificity respecting the qualitative analysis of scintigrams and renography curves. Clinical verification and standardization of more sophisticated quantitative parameters is mandatory in order to improve sensitivity and specificity as well as to overcome technical and physiological pitfalls of diuresis renography.

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