

Comparative Study of Color Doppler Voiding Urosonography Without Contrast Enhancement and Direct Radionuclide Voiding Cystography for Diagnosis of Vesicoureteric Reflux in Children

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Received July 7, 2011, from the Departments of Urology (M.M.F., M.F., M.A.) and Radiology (A.M.) and Genius and Talented Student Organization, Student Research Center (M.G.-R.), Urmia University of Medical Sciences, Urmia, Iran; and Blizard Institute of Cell and Molecular Science, Queen Mary, University, London, England (N.M.-S.). Revision requested July 13, 2011. Revised manuscript accepted for publication July 18, 2011.

We thank Thomas Down, PhD (Cambridge University, Cambridge, England), for invaluable help with statistical data analysis. This article was extracted from Dr Falahati's doctoral thesis for Urmia University of Medical Sciences.

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Abbreviations

NPV, negative predictive value; PPV positive predictive value

Objectives—Most available studies investigating the diagnostic accuracy of color Doppler voiding urosonography in the detection of vesicoureteric reflux used an echo contrast agent. It is unknown whether echo contrast agents are necessary for diagnosis or follow-up of vesicoureteric reflux. We compared color Doppler voiding urosonography without contrast enhancement and direct radionuclide voiding cystography in the detection and grading of vesicoureteric reflux with respect to the sex and age of patients as well as the severity of reflux.

Methods—In the 66 patients enrolled (56 girls and 10 boys), 132 renoureteral units were investigated. All patients underwent Doppler voiding urosonography and direct radionuclide voiding cystography within 3 hours. Direct radionuclide voiding cystography was used as the reference standard.

Results—Our results indicate good overall sensitivity (83%) and specificity (77%) for color Doppler voiding urosonography without contrast enhancement in comparison with direct radionuclide voiding cystography. As the age of the patients decreased, the sensitivity of urosonography increased, reaching 100% among patients younger than 1 year. In the comparison of different grades of reflux severity, we found that the sensitivity and specificity were elevated as the grade increased (both parameters reaching 100% in the most severe cases). Severity grading was equal between the two methods.

Conclusions—We have shown that Doppler voiding urosonography without contrast enhancement is a comparably reliable method versus direct radionuclide voiding cystography in the detection and grading of vesicoureteric reflux, especially at higher grades of reflux and in children younger than 1 year.

Key Words—children; color Doppler voiding urosonography; direct radionuclide voiding cystography; vesicoureteric reflux

Vesicoureteric reflux is the most common urinary congenital anomaly in children.^{1,2} It is defined as retrograde flow of urine from the bladder into the ureter and the renal collecting system. Its frequency ranges from 0.5% to 1.5% in the pediatric population. The precise clinical importance of vesicoureteric reflux remains undetermined, and the correlation between vesi-

coureteric reflux, urinary tract infection, renal scarring, and chronic renal failure is generally difficult to predict.³ However, vesicoureteric reflux predisposes children to pyelonephritis, which is the most common underlying cause of kidney damage among the pediatric population, and proper diagnosis and treatment of vesicoureteric reflux may prevent this complication.

Earlier methods routinely applied for the detection of vesicoureteric reflux include x-ray voiding cystourethrography and direct radionuclide voiding cystography.⁴ Comparative studies have shown that direct radionuclide voiding cystography in experienced hands is more sensitive for the detection of vesicoureteric reflux than x-ray voiding cystourethrography.⁵ However, both of these techniques involve exposure to ionizing radiation, although the exposure is lower in direct radionuclide voiding cystography. Given the risks associated with radiation exposure, there has been an increasing need for the introduction of radiation-free methods in recent years not only for diagnosis but also for follow-up of patients with vesicoureteric reflux. Doppler voiding urosonography is now considered a practical, safe, radiation-free modality.⁶ In response to the appeal of the American Urological Association for a decrease of radiation exposure in patients with vesicoureteric reflux, many studies have been conducted to assess the sensitivity and specificity of the above-mentioned methods.^{7–10} These findings showed that the sensitivity of Doppler voiding urosonography is comparable to or higher than that of direct radionuclide voiding cystography and x-ray voiding cystourethrography.

On the basis of conclusions of these studies, some authors suggest that sonography should be compared with direct radionuclide voiding cystography rather than to x-ray voiding cystourethrography.⁸ Recently, Bosio and Manzoni¹¹ reported on the assessment of the male posterior urethra with contrast-enhanced voiding cystourethrosonography and recommended this technique for initial detection of vesicoureteric reflux in both sexes. Giordano et al¹² also suggested using Doppler voiding urosonography as the first step in the diagnosis of vesicoureteric reflux in both boys and girls.

Most previous studies applied echo contrast agents for the detection of vesicoureteric reflux by either gray scale or color Doppler voiding urosonography. Previous findings indicate that a significant increase in the diagnostic accuracy of voiding urosonography can be achieved by using color Doppler imaging when compared with gray scale imaging.¹³ Although echo-enhancing agents were shown to be well tolerated by patients,¹⁴ it is not known whether their application is a necessity in all cases of vesicoureteric

reflux diagnosis and follow-up. Hence, in our study, we aimed to compare color Doppler voiding urosonography without contrast enhancement and direct radionuclide voiding cystography for the detection and grading of vesicoureteric reflux with respect to the sexes and ages of patients and the severity of the reflux.

Materials and Methods

Patients were enrolled between April and December 2010 in this cross-sectional study. Children were excluded if an ongoing active infection was present; urinary catheterization was not possible because of an anatomic defect; one or both kidneys could not be assessed by sonography; and parents did not give informed consent. Furthermore, 4 children were excluded for lack of compliance. A total of 66 patients completed the study (56 girls and 10 boys; age range, 3 months–11 years; median, 3.75 years). All patients were referred by a pediatric nephrologist or urologist for diagnostic imaging for suspected vesicoureteric reflux. The Institutional Review Board and Ethics Committee approved the study. The purpose and procedures of the investigation were fully explained, and written informed consent was obtained from the parents or guardians of the study participants.

The transurethral catheterization was performed by a urology resident in a sterile fashion with a Foley catheter appropriate for the patient's age. Girls were placed in a lithotomy position and boys in a supine position. Groin areas and genitalia were washed with povidine iodine, and 2% lidocaine gel was injected into the urethra 10 minutes before catheterization. Catheter balloons were filled with 3 to 5 mL of saline.

The following sonographic procedure was performed in all patients: First, conventional (gray scale) sonography of the kidney and urinary tract was performed to diagnose the size, shape, presence of hydronephrosis, scars, and parenchymal thickness and structure, followed by Doppler voiding urosonography. Then the bladder was filled with a normal saline injection of up to 30 to 40 cm H₂O or to the point when the patient felt the need to void.

Conventional and Doppler sonographic examinations were performed by a single sonographer using a Nemio 30 system (Toshiba Co, Ltd, Tokyo, Japan) equipped with a 3.5- to 5-MHz curved linear transducer. Power and color settings, the pulse repetition frequency, and the wall filter were set at the minimum range to detect flow with very low velocity. First, in a transverse position, the junction between the ureter and the bladder was acquired (Figure 1). Then each side was studied for at least 5 minutes with

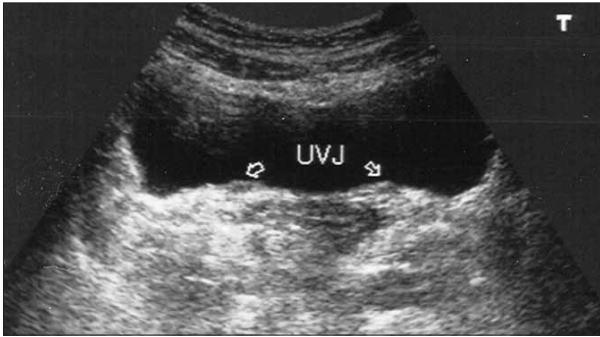


Figure 1. Transverse sonogram of bilateral urethrovesical junction (UVJ) projection at the base of the bladder.

probe rotation in a transverse oblique fashion to assess the urethrovesical junction and to observe whether a reversed urine jet from the bladder to the ureter was present.

After Doppler voiding urosonography, the patient was transferred to the nuclear medicine center with the urinary catheter in place. A total of 0.5 to 1 MCi of technetium Tc 99m phytate was injected into the bladder along with an amount of normal saline based on age. Dynamic images were obtained in the both filling and emptying phases (for which the Foley catheter was connected to a urine bag) with 10-second frames in 100 seconds using a single-head ADAC Genesys analog nuclear camera (Philips Healthcare, Andover, MA; Figure 2). All patients underwent Doppler voiding urosonography and direct radionuclide voiding cystography within 3 hours. Both the sonographer and the nuclear medicine radiologist were blinded to each other's results.

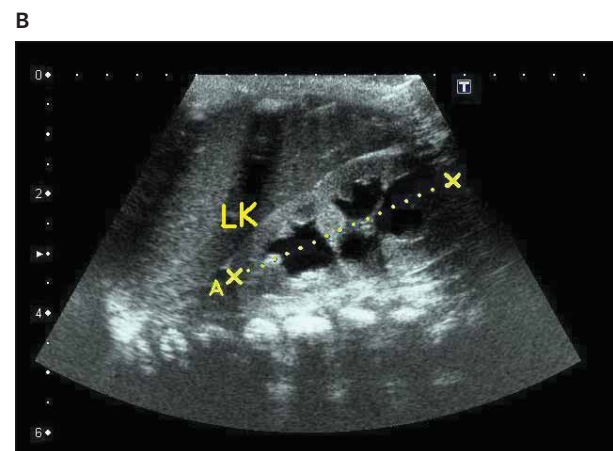
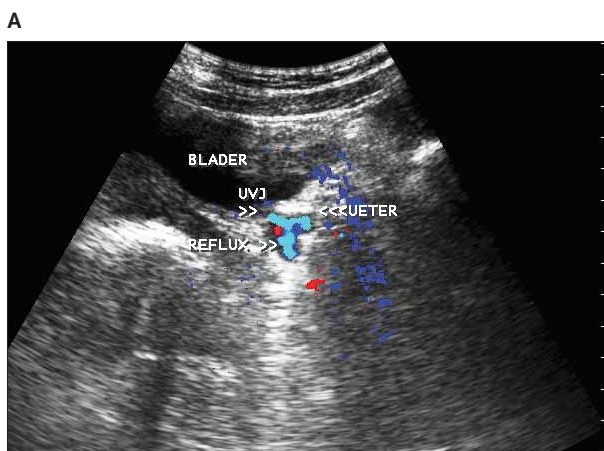
Statistical analysis was performed with SPSS version 16 software (SPSS Inc, Chicago, IL) and the R statistical package (<http://www.r-project.org>). The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) in groups of sex, age, and reflux severity were determined. Direct radionuclide voiding cystography was used as the reference standard. For the multivariate analyses, we performed logistic regression to examine the accuracy of Doppler voiding urosonography using age, sex, and reflux severity as factors of its accuracy. $P \leq .05$ was considered statistically significant.

Results

In the 66 patients enrolled, 132 renoureteral units were investigated. Children were divided into 3 age groups: younger than 1 year (13 patients), 1 to 5 years (29 patients), and older than 5 years (24 patients). On the basis of Doppler voiding urosonographic findings, vesicoureteric reflux was graded as mild (low-grade reflux without hydroureteronephrosis), moderate (reflux with mild to moderate hydroureteronephrosis; Figure 2), or severe (reflux with severe hydroureteronephrosis; Figure 3).

Vesicoureteric reflux was detected in 56 of the 132 renoureteral units (42%) by Doppler voiding urosonography (7 in boys and 49 in girls), whereas direct radionuclide voiding cystography showed reflux in 42 renoureteral units (32%; 5 in boys and 37 in girls). In 104 of the 132 renoureteral units (79%), Doppler voiding urosonography and direct radionuclide voiding cystography showed identical findings (either positive or negative for reflux); 35 renoureteral units had a positive diagnosis of reflux by both

Figure 2. A. Color Doppler sonogram of the urethrovesical junction (UVJ) on the left side showing reflux of urine into the left ureter (blue). **B.** Upper tract sonogram showing moderate hydronephrosis in the left kidney (LK; grade 2 reflux).



Doppler voiding urosonography and direct radionuclide voiding cystography, whereas 69 units had a negative diagnosis of reflux based on both methods.

The sensitivity, specificity, PPV, and NPV of Doppler voiding urosonography for the diagnosis of vesicoureteric reflux were 83%, 77%, 63%, and 91%, respectively. When comparing the results of Doppler voiding urosonography with direct radionuclide voiding cystography according to sex, the sensitivity, specificity, PPV, and NPV of Doppler voiding urosonography were 80%, 80%, 57%, and 92% in boys and 84%, 76%, 63%, and 91% in girls.

The sensitivity, specificity, PPV, and NPV of Doppler voiding urosonography in relation to the ages of the patients were 100%, 75%, 55%, and 100% for those younger than 1 year; 80%, 81%, 62%, and 92% for those 1 to 5 years of age; and 80%, 71%, 67%, and 83% for those older than 5 years. Further stratification of the accuracy of Doppler voiding urosonography based on age is shown in Table 1. When comparing Doppler voiding urosonography with direct radionuclide voiding cystography in relationship to the severity of the reflux, the sensitivity, specificity, PPV,

and NPV were 81%, 78%, 56%, and 89% for mild reflux; 89%, 99%, 89%, and 99% for moderate reflux; and all 100% for severe reflux. The severity grading was equivalent across the two methods (Table 1).

Linear regression analysis confirmed that the accuracy of Doppler voiding urosonography was dependent on age ($P < .0001$) and reflux severity ($P < .0001$). However, the accuracy was independent of the patient's sex ($P = .43$). There was a significant positive correlation between the reflux severity and the accuracy of diagnosis by Doppler voiding urosonography. Figure 4 shows a heat map of reflux severity measured with Doppler voiding urosonography and direct radionuclide voiding cystography.

Discussion

In comparison with most available studies, we aimed to assess the diagnostic efficacy of color Doppler voiding urosonography without the application of contrast enhancement. Although echo-enhancing agents were shown to be well tolerated by patients,¹⁴ their availability may be

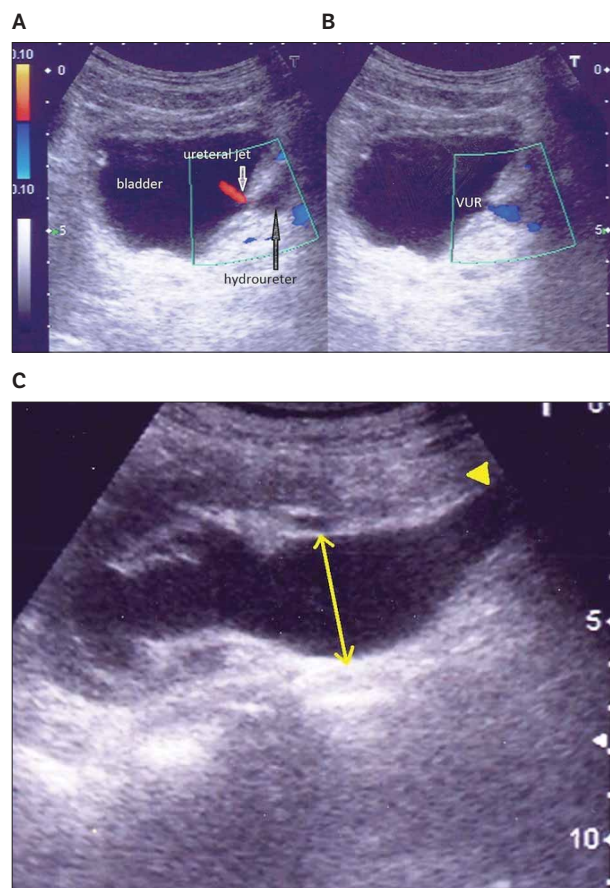


Figure 3. **A.** Color Doppler sonogram showing a dilated distal left ureter (black arrow) and a ureteral jet (red signal). **B.** Color Doppler sonogram showing vesicoureteric reflux into the distal left ureter (blue signal). **C.** Upper tract sonogram showing a severe hydroureter (arrowhead) and severe dilatation of the renal pelvis (arrow) accompanied by renal scarring. **D.** Direct radionuclide voiding cystogram during the filling phase from the posterior aspect showing backflow of isotopic material from the urinary bladder into the ureter and renal pelvis, which shows severe reflux.

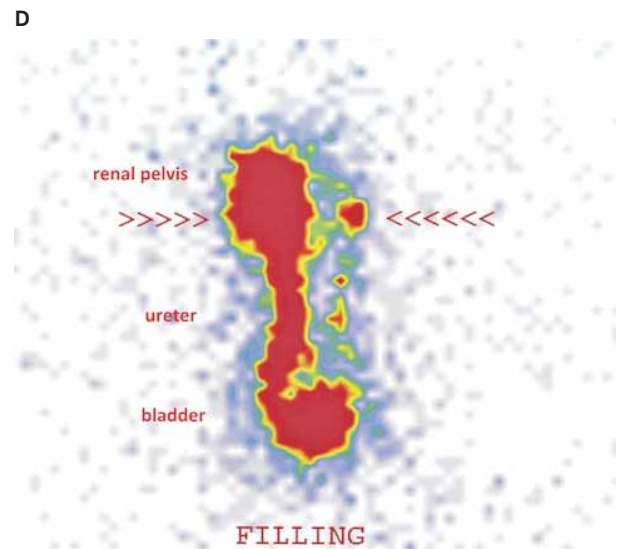


Table 1. Accuracy of Doppler Voiding Urosonography Based on Age

Age, y	Right-Side	Right-Side	Left-Side	Left-Side	Right-Side Reflux Category Correlation	Left-Side Reflux Category Correlation
	Reflux Correctly Detected With Urosonography	Reflux Detected With Urosonography but Not Found With Cystography	Reflux Correctly Detected With Urosonography	Reflux Detected With Urosonography but Not Found With Cystography		
1	100 (4/4)	22 (2/9)	100 (2/2)	27 (3/11)	100	100
1–5	88 (7/8)	9.5 (2/21)	75 (6/8)	14 (3/21)	100	100
>5	90 (9/10)	21 (3/14)	ND	ND	100	ND

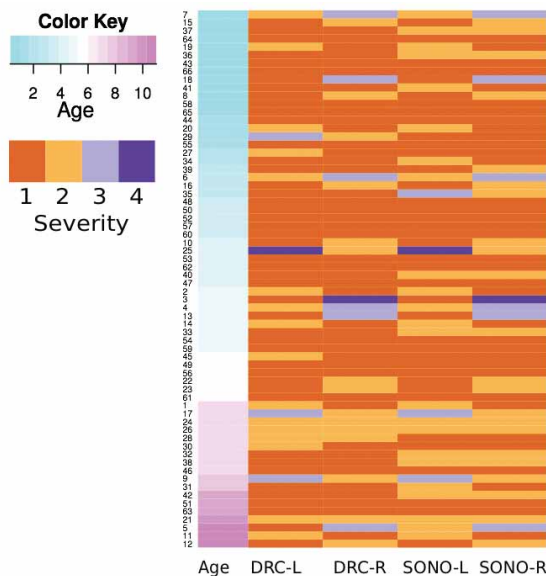
Values are percent (number) and percent as applicable. ND indicates not detected.

limited, and it is unknown whether their application is necessary in all cases of vesicoureteric reflux diagnosis and follow-up.

Both direct radionuclide voiding cystography and Doppler voiding urosonography have similar diagnostic capabilities and similar disadvantages. They offer low anatomic resolution and lack visualization of the urethra. Therefore, the initial diagnosis of vesicoureteric reflux in boys in whom examination of the urethra is of major importance usually still requires x-ray voiding cystourethrography.

Our results indicate good overall sensitivity (83%) and specificity (77%) for color Doppler voiding urosonography without contrast enhancement in comparison with direct radionuclide voiding cystography. The NPV was found to be relatively high (91%) in our study.

Figure 4. Heat map of vesicoureteric reflux severity measured with Doppler voiding urosonography (SONO) and direct radionuclide voiding cystography (DRC). Numbers on the vertical axis are patient numbers. L indicates left; and R, right.



The difference with respect to these parameters did not differ significantly between the sexes, and linear regression has shown that Doppler voiding urosonography is equivalently accurate in both sexes. However, when we compared the different age groups in our study, important differences were revealed. As the age of the patients decreased, the sensitivity and NPV of Doppler voiding urosonography increased, reaching 100% among patients younger than 1 year. This finding indicates that Doppler voiding urosonography has equal diagnostic accuracy as direct radionuclide voiding cystography in very young infants and thus is optimal for use in this population.

At the same time, the PPV increased as the age of the patients increased. This finding might partly be explained by better compliance of older patients. In the comparison of different grades of reflux severity, we found that all parameters (sensitivity, specificity, PPV, and NPV) improved as the grade increased (reaching 100% in all aspects in the most severe cases), clearly showing that a very accurate diagnosis can be obtained in more severe grades. Table 1 and Figure 3 also show the correlation between the two methods with respect to grade.

The use of echo enhanced renal sonography for detection of vesicoureteric reflux in children has already been successfully investigated in clinical trials.^{15,16} Kenda et al⁷ investigated 99 children with 198 potentially refluxing units simultaneously by direct radionuclide voiding cystography and echo-enhanced gray scale sonography. Their results were compared with direct radionuclide voiding cystography as the reference diagnostic test. They obtained similar overall sensitivity (79%), but higher specificity (92%) compared with our results. They also concluded that sonography represents a reliable diagnostic tool for detection and follow-up of vesicoureteric reflux. In a study by Ascenti et al,⁸ using color Doppler instead of gray scale sonography, direct radionuclide voiding cystography showed reflux in 54 of 128 renoureteral units, and voiding urosonography confirmed reflux in 44 (81%). They

also obtained higher specificity (97%) compared with our findings and also reported that for detection of more severe grades of reflux, the sensitivity of Doppler voiding urosonography reached 100%, which is concordant with our findings. They further suggested higher diagnostic accuracy of urosonography compared with direct radionuclide voiding cystography in determination of the reflux grade. A comparative study of the three most common modalities for vesicoureteric reflux assessment (ie, x-ray voiding cystourethrography, direct radionuclide voiding cystography, and Doppler voiding urosonography) by Piscitelli et al⁹ showed greater sensitivity and specificity for Doppler voiding urosonography compared with x-ray voiding cystourethrography in detecting reflux, approaching the levels of direct radionuclide voiding cystography, although that study used a contrast medium for sonography.

The comparison of our results with data available from previous studies indicates that the use of a contrast medium offers higher sensitivity for detection of vesicoureteric reflux at lower grades of the disease. However, in high grades of reflux, the diagnostic efficacy of color Doppler voiding urosonography without contrast is similar to that of direct radionuclide voiding cystography, currently regarded as the most sensitive method for reflux assessment. As the age of the investigated patients decreased in our study, the sensitivity and NPV of Doppler voiding urosonography increased, reaching 100% for both among patients younger than 1 year. On the basis of these considerations, we suggest that color Doppler voiding urosonography is a valuable diagnostic technique even without the application of contrast enhancement for follow-up of medium- to high-grade reflux, especially in younger children.

Taking into consideration the possibility that approximately half of the children referred for examination of possible reflux will have a negative diagnosis, it is even more important to use a radiation-free method for assessment of these patients. The high NPV of Doppler voiding urosonography described in previous studies and in our investigation, especially in younger children, indicates the reliability of this method in this respect.¹⁴

Similar to previously reported investigations, the total duration of the examination applying both direct radionuclide voiding cystography and Doppler voiding urosonography was about 20 to 30 minutes for each patient. Although this process might be regarded as time-consuming, one should not forget that a longer sonographic examination time also improves the probability of detecting intermittent reflux.

In conclusion, we have shown that Doppler voiding urosonography is a comparably reliable method versus direct radionuclide voiding cystography in the detection and grading of vesicoureteric reflux in children younger than 1 year and in older children especially at higher reflux grades, even without the application of echo contrast agents. If further research confirms our findings, we suggest Doppler voiding urosonography without contrast enhancement as an ideal tool for diagnosis of vesicoureteric reflux in children younger than 1 year and for follow-up of grade 2 and higher reflux in the general pediatric population.

References

1. Alon U, Pery M, Davidai G, Berant M. Ultrasonography in the radiologic evaluation of children with urinary tract infection. *Pediatrics* 1986; 78:58–64.
2. Kenda R, Kenig T, Silc M, Zupancic Z. Renal ultrasound and excretory urography in infants and young children with urinary tract infection. *Pediatr Radiol* 1989; 19:299–301.
3. Kljucvsek D, Kljucvsek T, Kersnik Levart T, Novljan G, Kenda RB. Catheter-free methods for vesicoureteric reflux detection: our experience and a critical appraisal of existing data. *Pediatr Nephrol* 2010; 25:1201–1206.
4. Fettich JJ, Kenda RB. Cyclic direct radionuclide voiding cystography: increasing reliability in detecting vesicoureteral reflux in children. *Pediatr Radiol* 1992; 22:337–338.
5. Polito C, Rambaldi PF, La Manna A, Mansi L, Di Toro R. Enhanced detection of vesicoureteric reflux with isotopic cystography. *Pediatr Nephrol* 2000; 14:827–830.
6. Darge K. Voiding urosonography with US contrast agent for the diagnosis of vesicoureteric reflux in children: an update. *Pediatr Radiol* 2010; 40:956–962.
7. Kenda RB, Novljan G, Kenig A, Hojker S, Fettich JJ. Echo-enhanced ultrasound voiding cystography in children: a new approach. *Pediatr Nephrol* 2000; 14:297–300.
8. Ascenti G, Zimbaro G, Mazziotti S, Chimenz R, Baldari S, Fede C. Vesicoureteral reflux: comparison between urosonography and radionuclide cystography. *Pediatr Nephrol* 2003; 18:768–771.
9. Piscitelli A, Galiano R, Serrao F, et al. Which cystography in the diagnosis and grading of vesicoureteral reflux? *Pediatr Nephrol* 2008; 23:107–110.
10. Koşar A, Yeşildağ A, Oyar O, Perk H, Gülsoy U. Detection of vesicoureteric reflux in children by colour-flow Doppler ultrasonography. *BJU Int* 2003; 91:856–859.
11. Bosio M, Manzoni GA. Detection of posterior urethral valves with voiding cystourethrosonography with echo contrast. *J Urol* 2002; 168:1711–1715.
12. Giordano M, Marzolla R, Puteo F, Scianaro L, Caringella DA, Depalo T. Voiding urosonography as first step in the diagnosis of vesicoureteral reflux in children: a clinical experience. *Pediatr Radiol* 2007; 37:674–677.

13. Valentini AL, Salvaggio E, Manzoni C, et al. Contrast-enhanced gray-scale and color Doppler voiding urosonography versus voiding cystourethrography in the diagnosis and grading of vesicoureteral reflux. *J Clin Ultrasound* 2001; 29:65–71.
14. Darge K, Troeger J, Duetting T, et al. Reflux in young patients: comparison of voiding US of the bladder and retrovesical space with echo enhancement versus voiding cystourethrography for diagnosis. *Radiology* 1999; 210:201–207.
15. Darge K, Dütting T, Zieger B, Möhring K, Rohrschneider W, Tröger J. Diagnosis of vesicoureteral reflux with echo-enhanced micturition urosonography [in German]. *Radiologe* 1998; 38:405–409.
16. Bosio M. Cystosonography with echocontrast: a new imaging modality to detect vesicoureteric reflux in children. *Pediatr Radiol* 1998; 28:250–255.