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## Voiding urosonography with ultrasonography contrast medium in children

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**Abstract** Voiding urosonography (VUS) with ultrasonography contrast medium is a new modality in the detection of vesicoureteral reflux (VUR) in children. The purpose of this study was to evaluate the diagnostic accuracy of VUS compared with voiding cystourethrography (VCUG) in the detection of VUR. One hundred and eighteen patients, aged 3 weeks to 16 years, with 234 ureterorenal units, were investigated by VUS with ultrasonography contrast medium and radiographic VCUG in one session. The indications were predominantly urinary tract infection and follow-up of previously detected VUR. During the sonographic examination, the bladder was filled with saline solution and an ultrasonography contrast medium (Levovist) was administered through a catheter. Reflux was diagnosed when echogenic bubbles were observed in the ureter or in the renal pelvis. Afterwards, conventional VCUG was performed. Concordant findings were obtained in 210 of 224 ureterorenal units (93.7%). Reflux was excluded by both methods in 174 units (77.7%). With the VCUG as the reference, the sensitivity of VUS was 90%, the specificity 94.6%, the positive predictive value 78.3%, and the negative predictive value 97.8%. The accuracy was 93.7%. In conclusion, VUS with ultrasonography contrast medium is a reliable diagnostic tool for the detection of VUR in children.

**Keywords** Voiding urosonography · Vesicoureteral reflux · Ultrasonography contrast media · Voiding cystourethrography

### Introduction

Vesicoureteral reflux (VUR) is a common abnormality in children. There is a correlation between VUR, urinary tract infection and reflux nephropathy [1]. Two methods are routinely used to identify VUR in children, namely radiographic voiding cystourethrography (VCUG) and radionuclide voiding cystography (RNC) [2, 3]. Trials to detect VUR by ultrasonography were undertaken to eliminate the radiation exposure intrinsic in nuclear or fluoroscopic cystography [4]. Clinical studies were performed using techniques such as color Doppler sonography [5, 6], filling the bladder with air [7], or the use of sonicated albumin in the detection of reflux [8, 9]. Several generations of ultrasonography contrast agents have been developed since then and the use of voiding urosonography (VUS) with ultrasonography contrast medium has already been successfully investigated in first clinical trials [10, 11, 12, 13, 14, 15, 16] comparing VUS and VCUG [10, 11, 12, 13, 15, 16] or RNC [14]. The aim of this study was to verify the value of VUS with ultrasonography contrast medium in the detection of VUR in a large population of children and to compare the results with the findings of the literature.

### Materials and methods

For this study, 118 children (90 females and 28 males), aged 3 weeks to 16 years (median 4 years and 6 months), with 234 ureterorenal units were recruited (2 patients after nephrectomy with one unit). All patients were referred for the evaluation of VUR. The indications for reflux examination were urinary tract infection ( $n=67$ ), follow-up of a previously diagnosed VUR ( $n=15$ ), sonographically diagnosed dilation of the urinary pelvicaliceal system or megaureter ( $n=20$ ), malformation syndromes with high probability of renal involvement ( $n=10$ ), and enuresis ( $n=6$ ). After explanation of the purpose and technique of the study, written informed consent was obtained from all parents or guardians. Exclusion criteria were no consent by the parents, galactosemia, ongoing urinary tract infection and unsuccessful sonographic examination caused by restless children. Boys younger than 1 year of age were excluded because the catheterization is difficult in this age

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group, and VCUg using suprapubic puncture is preferred in this group in our department. All patients received antibiotic prophylaxis (nitrofurantoin 3 mg/kg orally for 3 days). The study was approved by the appropriate medical ethics committee.

### Sonography

The initial examination was standard sonography of the urinary tract performed with the patient in the supine and prone position. Normal fluid intake was allowed prior to the examination. Baseline sonograms were obtained in two perpendicular planes of the kidney, ureters, and bladder. Attention was paid to findings in the retrovesical region, vesicoureteral junction, dilated ureter, and the renal pelvis. The examination was performed on an outpatient basis without sedation using an Acuson machine (Acuson 128 XP; Acuson, Mountain View, Calif., USA) with a 3- to 5-MHz curved array and 5- to 10-MHz linear transducers. The entire examination was videotaped on S-VHS video and documented by snapshots with laser camera. In order to keep the children younger than 5 years quiet, two people were necessary for VCUg as well as for VUS with ultrasonography contrast medium.

The sonography was followed by transurethral catheterization of the bladder in a standardized aseptic procedure with an infant feeding tube. The bladder was emptied and afterwards filled by drip infusion (prewarmed 0.9% physiological saline) with the top of the drip chamber 30–50 cm above the table. When the predicted bladder volume was reached or when the child began to show signs of urge to void, a suspension of the ultrasonography contrast medium Levovist (SH U 508A, Schering, Berlin, Germany) was instilled intravesically through the same catheter using a three-way stopcock. Levovist is a suspension of monosaccharide microparticles in sterile water consisting of 99.9% galactose and 0.1% palmitic acid. The presence of palmitic acid increased the echogenicity. These reflexive bubbles persist in the urinary tract for longer than Echovist, a suspension that can also be used as ultrasonography contrast medium. The suspension of Levovist (300 mg/ml solution) was prepared just before it was administered, as recommended by the manufacturer. After 2 min of equilibration, the contrast medium was manually injected into the bladder during visualization of both ureterovesical junctions by real-time sonography simultaneously. A small amount of Levovist was injected slowly at first, since too hasty filling of the bladder causes acoustic shadowing covering the retrovesical region [14]. The volume of the ultrasonography contrast medium administered was approximately 10% of the volume of the bladder filling. In children younger than 1 year, the maximal volume was 10 ml. In older children, repeated filling with Levovist was performed if contrast appeared insufficient. The microbubbles were stable for over 20 min after application, permitting enough time for an alternate examination in longitudinal and transverse sections of each flank in supine and prone positions prior to voiding. Afterwards, the child was asked to void with the catheter in place. This was used to visualize reflux at this stage of function. For this purpose the children were returned from the prone to the supine position. Babies voided in the prone as well as in the supine position. Uncooperative, young children were allowed to void spontaneously. The retrovesical parts of the ureters and the renal pelvis were scanned during voiding. The urethra was not visualized during the session.

### Voiding cystourethrography

Using the indwelling catheter, prewarmed saline solution and the X-ray contrast medium (Peritrist 400, Köhler-Chemie, Germany) were instilled into the bladder by drip infusion using the same volumes as in the sonographic examination. The procedure was monitored by fluoroscopy and spot-film documentation (Sirescop 5, Siemens, Erlangen, Germany) by one anterior-posterior spot film during filling and one in Lauenstein position during voiding for an assessment of the urethra.

### Adverse event monitoring

At the end of the examination, patients, depending on their age, were asked for symptoms they may have experienced, and all parents were instructed to contact the department if any symptoms appeared later.

### Study analysis

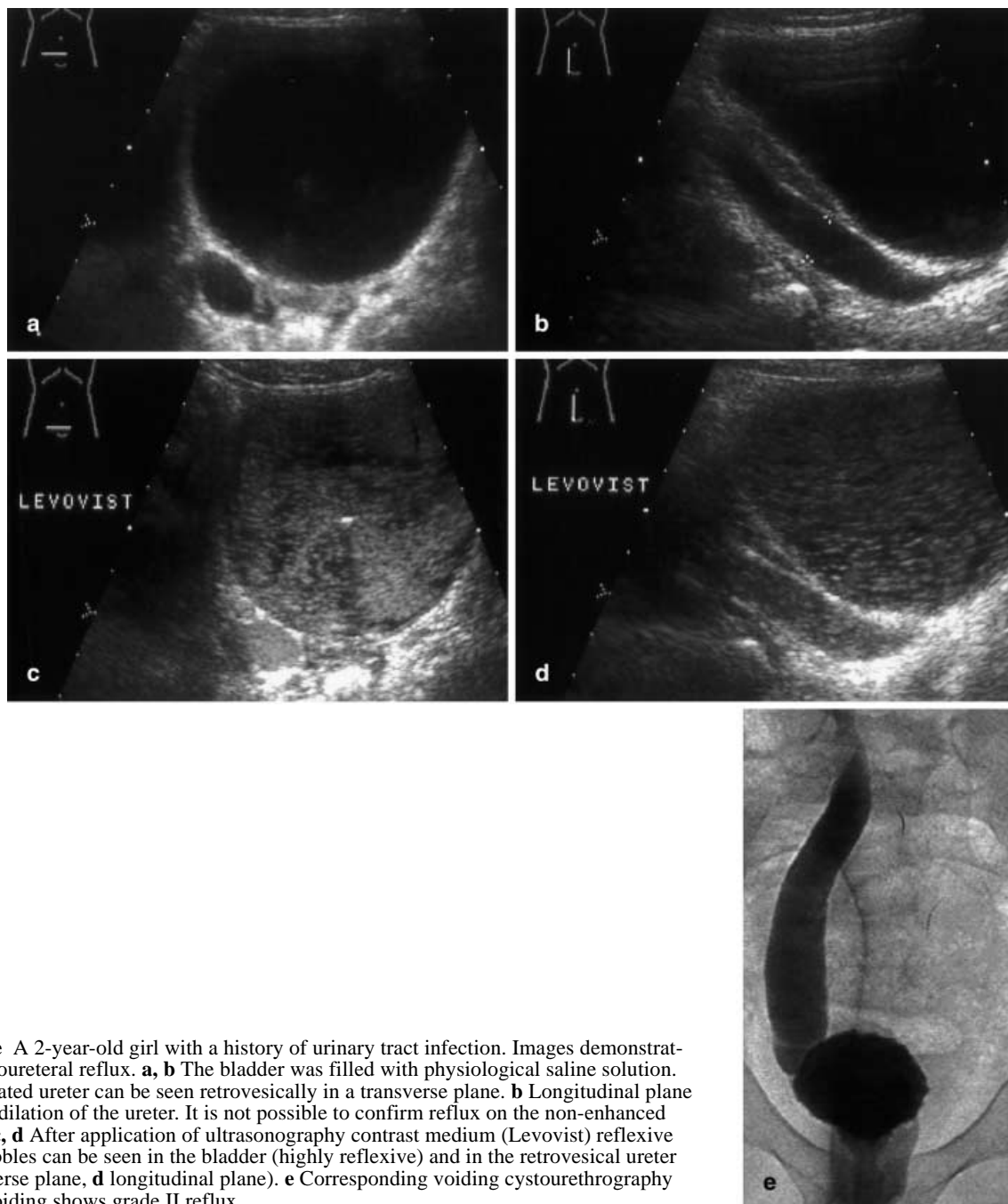
Reflux on VCUg was graded by the investigator immediately in accordance with the classification given by the International Reflux Study Committee (IRSC) [17]. Later, the videotapes of all ultrasonography studies were analyzed by two blinded reviewers. The two experienced pediatric radiologists were not acquainted with the results of the VCUg. Conclusions were made by consensus. Reflux on VUS with ultrasonography contrast medium was diagnosed when hyperechogenic bubbles were observed in the retrovesical ureter or in the upper tract, including the proximal ureter or renal pelvis. To make a comparative calculation in the study group, it was essential to assess the presence of reflux in terms of ureterorenal units rather than in terms of patients. Thus, a normal kidney with its own ureter was regarded as one ureterorenal unit. In cases of duplex kidneys they were counted as one unit. The findings in VUS with ultrasonography contrast medium were then graded in a similar manner to the IRSC classification [17]. The usual parameters of diagnostic tests (sensitivity, specificity, positive predictive value, negative predictive value, and accuracy) were calculated using VCUg as the reference standard.

## Results

During the study, 118 children were evaluated. Patients who voided during one examination and did not in the other were excluded from further analysis ( $n=5$ ). Thus, 113 children with 224 ureterorenal units were analyzed. In the VCUg, reflux was present in 40 ureterorenal units (17.9%) and excluded in 184 units (82.1%). Table 1 shows the ratio between positive and negative results of the VCUg and VUS with contrast medium. Taking VCUg as the reference standard, the sensitivity of VUS with ultrasonography contrast medium was 90% and the specificity was 94.6%. Positive predictive value was 78.3%, negative predictive value 97.8%, and accuracy 93.7%. In Table 2, the results of both methods are presented according to the grading of VUR [17]. The findings obtained from VUS with ultrasonography contrast medium and VCUg were consistent in 210 of 224 units

**Table 1** Comparison of voiding urosonography with ultrasonography contrast medium (VUS) and voiding cystourethrography (VCUG) in 224 ureterorenal units. For the evaluation of sensitivity, specificity, and predictive values of the sonographic evaluation, the voiding cystourethrography was used as the "gold standard" (PPV positive predictive value, NPV negative predictive value, Acc accuracy, Sens sensitivity, Spec specificity, + reflux, – no reflux)

Results of VUS	Results of VCUG		Total
	VCUG–	VCUG+	
VUS–	174	4	178 NPP 97.8%
VUS+	10	36	46 PPV 78.3%
Total	184 Spec 94.6%	40 Sens 90%	224 Acc 93.7%

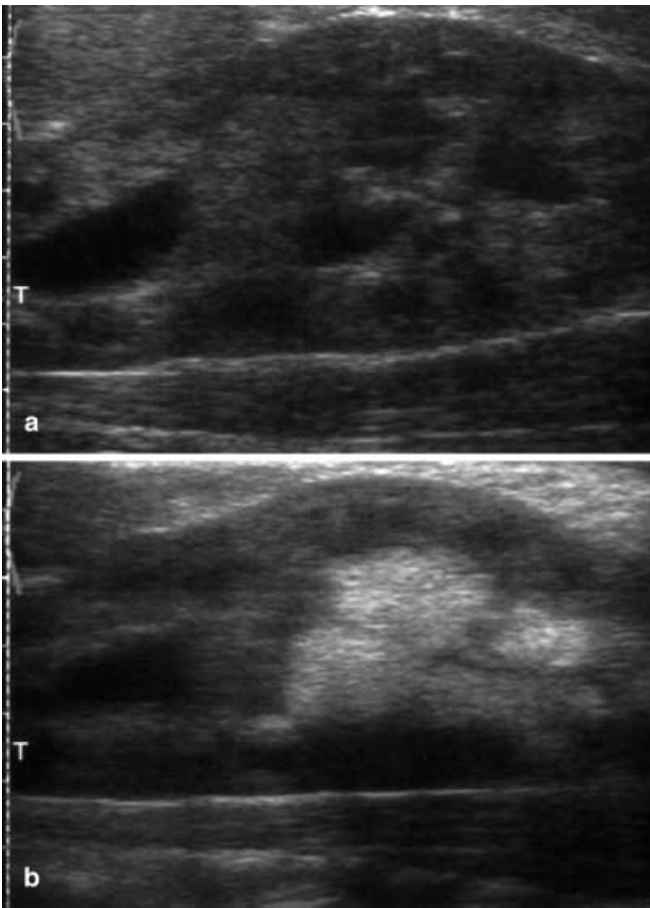


**Fig. 1a–e** A 2-year-old girl with a history of urinary tract infection. Images demonstrating vesicoureteral reflux. **a, b** The bladder was filled with physiological saline solution. **a** The dilated ureter can be seen retrovesically in a transverse plane. **b** Longitudinal plane showing dilation of the ureter. It is not possible to confirm reflux on the non-enhanced images. **c, d** After application of ultrasonography contrast medium (Levovist) reflexive microbubbles can be seen in the bladder (highly reflexive) and in the retrovesical ureter (**c** transverse plane, **d** longitudinal plane). **e** Corresponding voiding cystourethrography during voiding shows grade II reflux

**Table 2** Comparison of VUS with ultrasonography contrast medium and VCUG in 224 ureterorenal units. Grading of sonography and radiography was performed according to the Report of the International Reflux Study Committee [17]

VUS	VCUG					Total
	No reflux	Grade I	Grade II	Grade III	Grade IV/V	
No reflux	174	4	0	0	0	178
Grade I	5	10	1	0	0	16
Grade II	3	1	6	2	0	12
Grade III	1	0	0	8	0	9
Grade IV/V	1	0	0	1	7	9
Total	184	15	7	11	7	224





**Fig. 2a, b** A 4.6-year-old girl with high-grade vesicoureteral reflux in the lower part of a duplex kidney. **a** Baseline sonogram (longitudinal plane) shows dilated renal pelvis in the upper part and dilated calyces in the lower part of duplex kidney. **b** After application of Levovist the sonogram shows reflexive microbubbles dilating the renal pelvis and calyces in the lower part of the kidney, indicating high grade reflux. No enhancing substances could be detected in the upper part

(93.7%). No reflux was detected in 174 ureterorenal units by both methods (77.7%). Consistent findings compatible with a reflux grade I were obtained in 10 ureterorenal units, grade II in 6 units, grade III in 8 units, and grade IV–V in 7 units. Reflux in 10 ureterorenal units was only detected in the VUS. This included reflux grades I–V. In 4 ureterorenal units, all grade I refluxes, VCUG was positive and the corresponding VUS was negative. Discrepancies in the grading of reflux ( $n=36$ ) were seen in 5 units (13.9%). Figs. 1 and 2 show examples of corresponding reflux in sonography and the radiographic investigation.

All patients tolerated the catheterization well without complications during the examination or in the follow-up period from 3 days to 2 weeks. There were no negative side effects of the applied ultrasonography contrast medium.

## Discussion

The ideal method for the evaluation of VUR, especially in children, is one that is accurate, safe, without radiation, and non-invasive [12]. There are some reports describing the diagnostic regime using VUS with ultrasonography contrast medium in the detection of reflux [10, 11, 12, 13, 14, 15, 16].

The comparison of VUS with ultrasonography contrast medium with VCUG showed a 90% sensitivity and 94.6% specificity in detecting reflux in our study, with the largest number of patients published to date. Satisfactory results for sensitivity have been obtained previously in smaller studies with the same patients having the various diagnostic modalities in one examination session [10, 12, 13, 15, 16]. In a study using Echovist (in 18 patients) or Levovist (in 40 patients) as ultrasonography contrast medium, the comparison of VUS and VCUG showed 100% sensitivity and 86% specificity [10]. In a direct comparison of VUS with ultrasonography contrast medium and VCUG in 76 ureterorenal units, Darge et al. [12] reported a sensitivity of 100%, specificity of 97%, positive predictive value of 90%, and negative predictive value of 100% for the detection of VUR. Mentzel et al. [13] showed a sensitivity of approximately 92% and a specificity of 93%. In a study of young children (between birth and 5 years) with 98 ureterorenal units, the sensitivity was only 69%, but the specificity was 94%. They reported a rate of 9 of 98 units where reflux was only detected by VUS and not by VCUG [15]. The negative predictive values in all studies (between 95% and 100%) recommend VUS with ultrasonography contrast medium as the method for the exclusion of VUR. Recently, Valentini et al. [16] compared gray-scale VUS with ultrasonography contrast medium and color Doppler VUS with VCUG, and observed a higher diagnostic accuracy with the color Doppler VUS method (96%) than with the gray-scale method (90%). They hypothesized that the use of color Doppler imaging improves the accuracy of VUS with ultrasonography contrast medium. A study with lower sensitivity (79%) but similar specificity (92%) was published recently [14]. Unlike all other studies, in this study, RNC was used for the comparison and not VCUG. The possibility for screening kidney and bladder throughout the bladder filling for a long time helped to explain the finding of “false-positive” results in the 7 units of our population as well as in the results of the literature [11, 12, 13, 14]. However, it may also be that, as in RNC [3, 18], more refluxes are detected with VUS with ultrasonography contrast medium due to the ability to visualize single microbubble aggregates in a dilated renal pelvis. The main disadvantage of VUS with ultrasonography contrast medium in the detection of reflux is that an assessment of the urethra is not possible [13]. Therefore, no information about infravesical obstruction or urethral valves can be given. Bosio [10] reported urethral examination in boys using retrograde application of ultrasonography contrast medium or during the voiding phase, but this examination is difficult to

perform routinely. A further disadvantage of VUS with ultrasonography contrast medium is the cost of contrast media, which are much more expensive than X-ray contrast media.

Recognizing that most of our population referred for examination of VUR have had a negative diagnosis, we placed emphasis on screening these cases by VUS. The high negative predictive value of VUS with ultrasonography contrast medium reported in the literature confirms the reliability of this method [11, 12, 13, 14, 15, 16]. Boys undergo radiographic VCUG primarily in the first examination, especially in cases of phimosis with difficulties in catheterization, and if an assessment of the urethra is necessary. Further indications for VCUG as the first examination are an inadequate sonographic visualization of the bladder or the kidneys in the precontrast ultrasonography examination. Children suspected of voiding abnormalities undergo urodynamic studies. Urethral pathology that would require intervention is rare in girls. Hence, we recommend using VUS with ultrasonography contrast medium as the modality of choice in girls with suspected reflux and in follow-up of cases with known reflux. In cases with reflux only into the retrovesical ureter, no VCUG is needed. If reflux up to the renal pelvis is detected by VUS with ultrasonography contrast medium, a standard VCUG is also needed in girls, especially for assessment of the urethra and the voiding phase. This indication was established with the urological or surgical management option in mind. In a recently published paper, Darge et al. [19] ask why a VCUG should be performed in “non-symptomatic” girls with VUR into the non-dilated kidney who are undergoing chemoprophylaxis. According to this paper, we recommend using VUS with ultrasonography contrast medium as the first modality in the screening of high-risk patients for VUR (children and siblings of patients with VUR, renal transplants). However, VUS using an ultrasonography contrast medium allows reduction of the number of radiographic VCUG procedures in a large proportion of cases.

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