3D/4D contrast-enhanced urosonography (ceVUS) in children – is it superior to the 2D technique?

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Abstract

Background: By now, two-dimensional contrast-enhanced voiding urosonography (ceVUS) has become a well-established method for the diagnosis and treatment monitoring of vesicoureteral reflux in children, particularly after the recent approval for this application in children in the USA and in Europe. The introduction of three-dimensional static (3D) and real-time (4D) techniques with ultrasound contrast agents opens up new diagnostic opportunities for this imaging modality. **Objective:** To analyze whether 3D and 4D ceVUS is a superior technique compared to standard 2D ceVUS in diagnosing vesicoureteral reflux in children. **Material and methods:** The study included 150 patients (mean age 3.7 years) who underwent 2D and 3D/4D ceVUS for the diagnosis and grading of vesicoureteral reflux. **Results:** 2D ceVUS and 3D/4D ceVUS diagnosed the same number of vesicoureteral refluxes, however, there was a statistically significant difference in grading between the two methods. Performing 3D/4D ceVUS resulted in changing the initial grade compared to 2D ceVUS in 19 out of 107 refluxing units (17.76%) diagnosed. The 4D technique enabled a more conspicuous visualization of vesicoureteral reflux than the 3D technique. **Conclusions:** 2D ceVUS and 3D/4D ceVUS diagnosed the same number of vesicoureteral refluxes, however, there was a statistically significant difference in grading between the two methods. Thus 3D/4D ceVUS appears at least a valid, if not even a more conspicuous technique compared to 2D ceVUS.

Introduction

Two-dimensional (2D) contrast-enhanced voiding uro-sonography (ceVUS) has had a well-established position in the diagnosis and treatment monitoring of vesicoure-teral reflux (VUR) in children for over 15 years[1]. Already in 2001, it was shown that the technique allows to reduce by over one half the number of pediatric patients exposed to ionizing radiation during the diagnosis and treatment of VUR[2]. The method has proven its high effectiveness in the identification and grading of VUR and the assessment of the entire urinary tract in children, including the urethra[3–11]. Numerous reports indicate that ceVUS with the use of a sulfur hexafluoride contrast agent (SonoVue®, Bracco, Milan, Italy) is a highly sensitive and specific method, which can in many cases replace voiding cysto-urethrography (VCUG) or isotope cystography[3–6,8,10,12–15]. It is also considered a very safe procedure[16–18]. The modality has been additionally shown to be feasible for intraopera-tive use during endoscopic treatment of VUR in children[19].

Moreover, the latest technological innovations such as three-dimensional static (3D) and real-time (4D) tech-niques in combination with ultrasound contrast agent (UCA) options have opened up new possibilities for con-trast-enhanced urosonography; it has also been suggested by a preliminary study that these techniques may reveal additional information leading to a change in VUR grading compared to the 2D technique and a higher VUR detec-tion rate compared to VCUG – as already shown for 2D ceVUS[20].

The purpose of this study was to analyze whether 3D/4D ceVUS is a superior technique compared to standard 2D ceVUS in diagnosing VUR in children using a larger study group.

Material and methods

The study group comprised 150 consecutive pediatric pa-tients referred for ceVUS to the Department of Pediatric Radiology, Medical University of Lublin, Poland. Inclu-sion criteria to the present study involved recurrent uri-nary tract infections to be assessed for VUR and examina-tions in children with diagnosed VUR in order to monitor the effects of treatment. The exclusion criteria involved the lack of consent to ceVUS, urinary incontinence and coexisting abnormalities of the urogenital tract such as ureterocele, ectopic ureters, posterior urethral valves, neurogenic bladder due to myelomeningocele and other inborn abnormalities.

The study was performed after approval of the local eth-ics committee and obtaining signed informed consent from the parents of all patients, who had been previously informed about the aim of the study, the advantages and disadvantages of the method, and the off-label use of the contrast agent (sulfur hexafluoride, SonoVue®, Bracco, Mi-lan, Italy) in children at the time of scanning. Currently the contrast agent is registered for the use in children.

All patients underwent ceVUS with SonoVue® as the UCA and a combined approach of different sonographic tech-niques (2D, 3D and 4D ultrasound) and various anatomi-cal accesses, performed before, during and after intravesi-cal UCA solution administration in all the patients[20]. No special preparation or sedation was applied. The examina-tions were performed using a GE Voluson E8 ultrasound scanner (GE Healthcare, USA) with a pediatric micro con-vex real-time 4D transducer RNA5-9-D (5–9 MHz) and GE Voluson E8 Expert scanner (GE Healthcare, USA) with an endovaginal convex real-time 4D transducer RIC5-9-D (5–9 MHz).

Initially, each patient underwent a comprehensive trans-abdominal and transperineal ultrasound examination of the urinary tract with the use of B-mode, Color Doppler and harmonic imaging modes according to the procedural recommendations in paediatric uroradiology issued by the European Society of Paediatric Radiology (ESPR)[21]. The results of these examinations were not analyzed in the cur-rent study.

Subsequently, all patients underwent ceVUS according to the procedural recommendations of the ESPR and Euro-pean Society of Urogenital Radiology (ESUR) with the use of a standard two-dimensional technique (2D ceVUS) with drip infusion of a saline-contrast agent solution (1.2 ml of SonoVue in 500 ml of saline)[21,22]. In all patients the exami-nation was subsequently complemented by static (3D) and real-time (4D) imaging of the ureters and the kidneys as well as by transperineal scans of the urethra during void-ing according to the previously described protocol[20]. The assessment of the urethra was not analyzed in the current study.

The consecutive stages of the examination were recorded as image files (JPG), video clips (AVI) and 3D/4D DICOM format files available for further post-processing if needed. On average, the examination lasted from 30 to 45 minutes.

All acquired 3D/4D data volumes have been post-processed using various tools such as rotating (in order to present the pelvicalyceal systems in their anatomical position), vol-ume rendering (to enhance the three-dimensional percep-tion of VUR and thus facilitate the understanding of the image), zooming (to present VUR in detail), sharpening (to enhance the margins of the pelvicalyceal system) and contrasting the image as well as removing artifacts (to in-crease the contrast between the VUR and its background, which enables a more pronounced and obvious presenta-tion of VUR, facilitating its grading). Post-processing was performed retrospectively directly after the examination. The chosen best 3D or 4D acquisition for each kidney was post-processed in the case of VUR. In the case of 4D clips used for post-processing, the 4D video clip was reviewed and the best frozen 4D image was further post-processed. The report included printed images and a detailed account of the basic ultrasound examination and ceVUS, including the description of the urethra. The post-processed images of VUR were printed in color on photographic paper, en-abling high-quality documentation.

Grades of vesicoureteral reflux	Number of refluxes detected by 2D ceVUS	Number of refluxes detected by 3D/4D ceVUS
0	193	193
I	1	1
II	39	29
III	38	41
IV	24	29
V	5	7
Total	300	300

Tab. 1. *Number and grades of vesicoureteral refluxes detected by 2D and 3D/4D contrast-enhanced voiding urosonography (ceVUS)*

A modified five-grade classification of Darge and Troeger[7,23] was used to identify the grade of VUR both in 2D and 3D/4D ceVUS.

All the examinations and analyses were performed by a single investigator, a pediatric radiologist with 15 years of experience, specializing in 2D and 3D/4D pediatric ultrasound, and who has performed ceVUS for over eleven years.

The statistical analysis including descriptive statistics, a t-test and chi-square test was performed using Statistica® (StatSoft, Tulsa, USA) software, version 10.0.

Results

The study group included 150 children: 101 girls and 49 boys (mean age 3.7 years old, SD ± 2.7 years, range 5 months to 11.3 years) examined between July 2015 and August 2017. All the patients underwent ceVUS with the use of SonoVue®.

Out of the 150 examined patients and 300 (100%) pelvi-ureteral units (PUU), basic 2D ceVUS diagnosed VUR in 76 patients, unilateral in 45 and bilateral in 31 cases (107 VURs; 35.67%) (Tab. 1).

3D/4D ceVUS diagnosed the same number of VURs as 2D ceVUS (Tab. 1). However, there was a statistically significant difference in grading between the two methods. Due to more detailed and three-dimensional visualization of VUR, 3D/4D ceVUS facilitated reflux grading, which resulted in changing the initial grade compared to 2D ceVUS in 19 out of 107 VURs (17.76%) diagnosed (Tab. 2).

Out of 107 (100%) VURs diagnosed by 3D/4D ceVUS in 105 (98.13%) cases 4D acquisition and in 2 (1.87%) cases 3D acquisition were chosen for post-processing as better visualizing VUR due to a smaller amount of motion artifacts and more detailed presentation.

3D/4D ceVUS appeared significantly better than 2D ceVUS in the morphological assessment of VUR, demonstrating the demarcation of the renal pelvis and the calyceal contours in more detail, with higher conspicuity and with higher contrast.

2D ceVUS	3D/4D ceVUS						
	Grade 0	Grade I	Grade II	Grade III	Grade IV	Grade V	
Grade 0	193						193
Grade I		1					1
Grade II			29	10			39
Grade III				31	7		38
Grade IV					22	2	24
Grade V						5	5
	193	1	29	41	29	7	**300**

Tab. 2. *Concordance between 2D ceVUS and 3D/4D ceVUS in the detection and grading of reflux. Green – refluxes diagnosed by both methods at the same grade. Yellow – refluxes graded differently by 2D ceVUS compared to 3D/4D ceVUS*

Discussion

The results of this study show that there were statistically significant differences in grading in 19 (17.76%) VURs where 3D/4D ceVUS diagnosed a higher grade than 2D ceVUS (Fig. 1; Fig 2). All 19 VURs were evaluated as grades II ($n = 10$), III ($n = 7$) or IV ($n = 2$) by 2D ceVUS, and as grades III, IV or V by 3D/4D ceVUS, respectively. VUR grading is one of the factors that may be an indication for surgery and thus changes in grading may impact on therapeutic decisions. Considering that endoscopic treatment is an option for all children with low grades of VUR (II/III), while surgical correction should be considered in patients with persistent high-grade VUR (grades IV/V)[24], differences in grading between 2D ceVUS and 3D/4D ceVUS may influence the choice of treatment and thus may be clinically relevant.

The results of the study show that 3D/4D ceVUS delivers a more detailed image of VUR than 2D ceVUS, thus allowing for easier and more accurate VUR grading. Owing to post-processing options which include rotating the image, rendering, sharpening, contrasting, zooming as well as removing artifacts, the volumetric technique (3D/4D ceVUS) allows for the presentation of VUR in a much clearer and more conspicuous way, with highly visible margins of the pelvicalyceal system and ureter, well visible due to increasing of the contrast, without artifacts and surrounding structures. Moreover, a multi-dimensional visualization of VUR inaccessible to the 2D technique enables a more precise and easier assessment of pelvicalyceal dilatation, thereby allowing a more accurate VUR grading that is much easier, more confident and faster than VUR identification using 2D ceVUS with the same equipment. This is particularly important in patients with abnormal renal rotation.
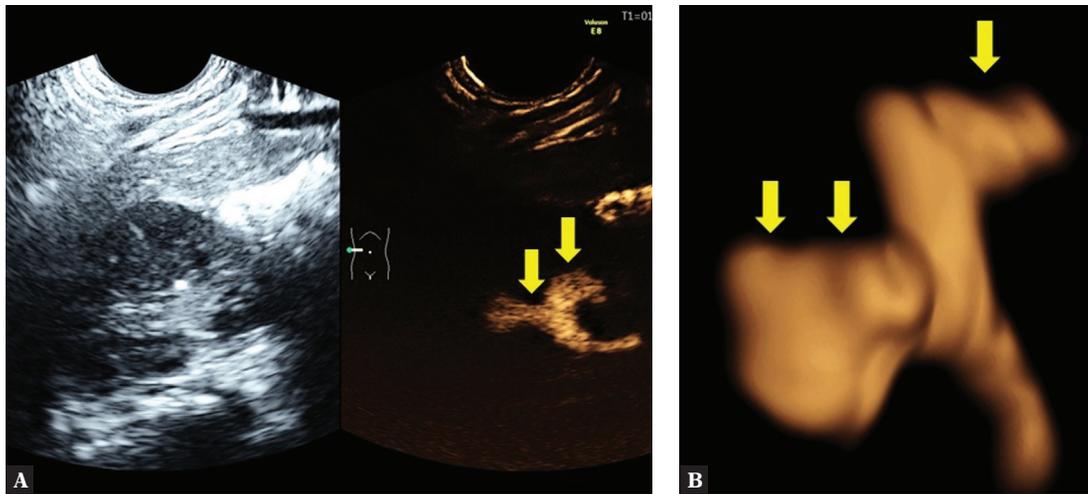
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Fig. 1. *Right-sided VUR in a three-year-old female patient with recurrent urinary tract infections.* **A.** *Two-dimensional contrast-enhanced voiding urosonography (2D ceVUS) in dual mode; simultaneous real-time images using both techniques, gray-scale (B-mode) on the left side and contrast-specific on the right side. Non-dilated renal pelvis and renal calyces (arrows) assessed as VUR grade II.* **B.** *Three-dimensional real-time contrast-enhanced voiding urosonography (4D ceVUS) post-processed volume image. Well-demarcated contours of a non-dilated renal pelvis and moderately dilated renal calyces (arrows) assessed as VUR grade III. More detailed and three-dimensional visualization of the reflux enabled more accurate reflux grading resulting in changing the initial grade compared to 2D ceVUS*

The opportunity to present VUR in the anatomical directions of the kidneys as in VCUG is a considerable advantage of the 3D/4D technique making the documentation more understandable and demonstrative for referring physicians, and also more objective and thus more reliable.

However, it is important to underline that 2D ceVUS still remains the basic ultrasound modality for VUR identification and grading. Only when using dual mode, e.g. simultaneous gray-scale 2D B-mode and contrast-specific images is it possible to reliably identify VUR, since dual mode helps to visualize the anatomy and to avoid artifacts (e.g. from other air- or gas-filled structures such as the bowel etc.), which cannot be achieved by 3D/4D US. B-mode 2D ceVUS is also a superior technique in the identification of VUR grade I.

In the current study both 3D and 4D techniques were used in all patients; however, the 4D technique appeared to be a more useful modality than 3D, enabling a better visualization of VUR in over 98% cases, probably due to the faster acquisition, however, with the intrinsic loss of resolution/voxel size. The main limitations of the 3D modality are its static character and higher susceptibility to artifacts, whereas the 4D technique, thanks to its real-time dynamic character, offers the possibility of a longer observation period allowing for imaging dynamic processes such as VUR, which can sometimes be visualized only temporally. Real-time scanning (4D) is particularly advantageous in children, in whom a lack of cooperation often creates difficulties in obtaining good quality acquisition, particularly considering that it includes all the features of the static (3D) technique and additionally offers further advantages as the dynamic modality. Thus, there is no need to use both techniques, since it prolongs the procedure without adding any major benefits.

Nevertheless, it is important to underline that the study has been performed entirely with the use of a single type of scanner and transducers of a single manufacturer, and thus there is a possibility that the assumptions applied and the results obtained in this study may be valid for this specific high-end equipment and transducers, but may differ for other equipment and other types of transducers.

Moreover, the subtle differences in grading between 2D and 3D/4D ceVUS may be partially caused by the quality of the transducers, due to the fact that a 3D/4D transducer may potentially have better quality compared to the 2D transducer used in this study. The differences in grading between 2D ceVUS and 3D/4D ceVUS may also result from the varying nature of VUR as its degrees may change quickly in time; thus, it is also possible that the observed differences between 2D examinations and the subsequently performed 3D/4D ceVUS may be in part explained and caused by this phenomenon, as both types of examinations cannot be performed in parallel, but one after another.

The limitations of 3D/4D ceVUS include very limited access to scanners offering high-quality 3D/4D imaging with the UCA option, longer duration of the examination compared to 2D ceVUS, and the need for post-processing. The scarce availability of high-end ultrasound scanners equipped with the 3D/4D contrast mode, as well as the relatively long learning curve for the technique, particularly regarding post-processing, significantly limit the possibility of introducing 3D/4D ceVUS into the diagnostic algorithm for VUR in children as a standard technique used routinely.

A review of the literature does not reveal any previously published studies by other authors using 3D or 4D ultrasound technique in ceVUS; thus, we cannot compare the obtained results with other authors. The results obtained in
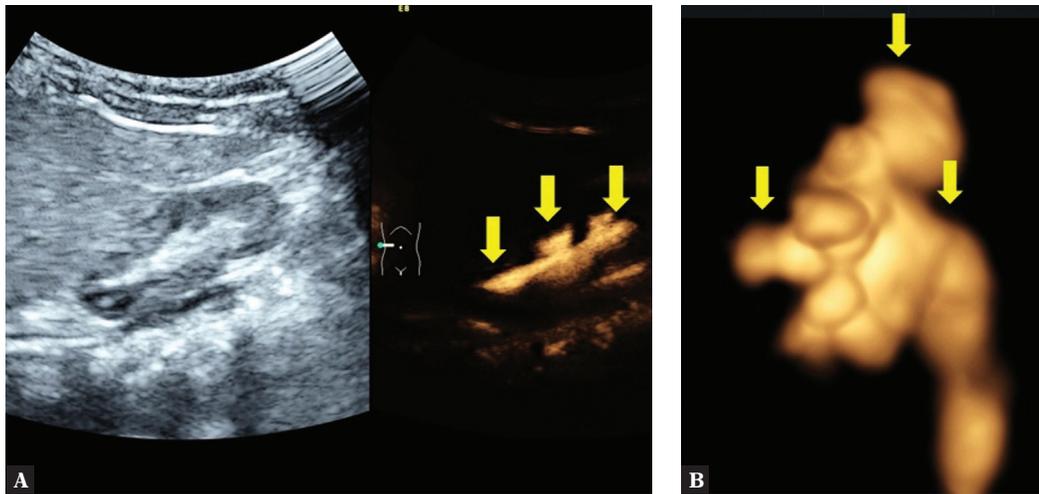
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Fig. 2. *Right-sided VUR in a two-year-old male patient persisting after treatment. **A.** 2D ceVUS in dual mode; simultaneous real-time images using both techniques, gray-scale (B-mode) on the left side and contrast-specific on the right side. Non-dilated renal pelvis and moderately dilated renal calyces (arrows) assessed as VUR grade III. **B.** 4D ceVUS post-processed volume image. Well-demarcated contours of a dilated renal pelvis and renal calyces (arrows) assessed as VUR grade IV. More detailed and three-dimensional visualization of the reflux enabled more accurate reflux grading resulting in changing the initial grade compared to 2D ceVUS*

this study are concordant with the results of a previously published study by the same authors[20]. It is, however, important to underline that the present study was performed on a larger group (150 patients) in comparison to the previous study (69 patients).

Pichler *et al*. used 4D US for the evaluation of the position of a bulking agent in children who had undergone endoscopic therapy of VUR. In their study, only children with postoperative urinary tract infections and/or a non-orthotopic position of the bulking agent were referred for VCUG. 4D US seemed to be a sufficient protocol in the follow-up of children after endoscopic treatment of low-grade VUR[25].

Other relevant limitations of this study include the non-blinded character of the study, patient recruitment at a single institution, and the involvement of a single pediatric radiologist. Thus, further multicenter prospective controlled blinded studies comparing 2D ceVUS with 3D/4D ceVUS are necessary.

Conclusion

In conclusion, the results of the current study indicate that 3D and 4D ceVUS demonstrated all VURs seen on 2D ce-

VUS. However, due to some additional information from display and rendering as well as postprocessing the 3D/4D technique led to a change in VUR grading compared to the standard 2D technique, showing higher grades than 2D ceVUS in some of the children with VUR. Moreover, 3D/4D ceVUS is the only modality offering multi-dimensional volumetric presentation of VUR, facilitating grading and increasing the quality of the documentation. The 4D technique, as a real-time dynamic modality, visualizes VUR better than the 3D technique, and thus can be used as the sole volumetric technique preceded by 2D ceVUS. Due to all the advantages listed above 3D/4D ceVUS appears to offer a superior and more conspicuous visualization and documentation as well as easier VUR grading compared to 2D ceVUS.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organizations, which might negatively affect the content of this publication and/or claim authorship rights to this publication.

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