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ORIGINAL ARTICLE **CME**

Contrast-enhanced Voiding Urosonography with Second-generation Ultrasound Contrast Agent versus Micturating Cystourethrogram for Diagnosis of Vesicoureteric Reflux

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ABSTRACT

Objective: *To review the performance of contrast-enhanced voiding urosonography (ceVUS) and micturating cystourethrogram (MCU) in diagnosing vesicoureteric reflux (VUR), and to evaluate the safety profile of ceVUS and the relevant imaging findings.*

Methods: *We retrospectively reviewed all patients who underwent both ceVUS and MCU in the same setting between August 2016 and May 2017. All ceVUS were performed with Philips Affiniti 70 ultrasound system. SonoVue was used as the contrast agent for ceVUS. All the patients then received MCU under fluoroscopic screening using iodinated contrast. Follow-up phone interviews were done up to 5 days after the examination.*

Results: *In total, 22 patients, including 18 male and four female patients (age range, 19 days to 24 months) were included, giving a total of 44 pelvi-ureteric units (PUUs) examined. VUR was detected in four out of the 44 PUUs. Except for one PUU which showed grade 2 VUR on ceVUS but grade 1 VUR on MCU, all other PUUs showed concordant findings on both examinations. Regarding detection of VUR irrespective of its severity, ceVUS showed sensitivity of 100% and specificity of 100% in our cohort. Other findings included: hydronephrosis (n=10), ureterocoele (n=1), multicystic dysplastic kidney (n=1), renal cysts (n=3), and urethral diverticulum (n=1). All the patients tolerated the procedures well with no significant complications from the procedures.*

Conclusion: *ceVUS is accurate, safe, and allows one-stop anatomical and functional assessment. Our unique case of urethral diverticulum detected on ceVUS also expanded our understanding in the utility of ceVUS for urethral pathology.*

Key Words: *Urinary bladder; Urinary tract infections*

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Ethics Approval: This study was approved by institutional review board (Ref: HKECREC-2017-046). Informed consent was obtained from patients' parents and / or guardians for the examination. The requirement of informed consent for publication of results was waived by the institutional review board.

中文摘要

第二代超聲造影劑進行的造影增強排尿性尿道超聲波造影（ceVUS）與排尿性透視膀胱尿道攝影（MCU）在膀胱輸尿管反流的診斷

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目的：比較造影增強排尿性尿道超聲波造影（ceVUS）和排尿性透視膀胱尿道攝影（MCU）在診斷膀胱輸尿管反流（VUR）中的表現，並評估ceVUS的安全性和相關影像學特徵。

方法：我們回顧分析由2016年8月至2017年5月期間同時接受ceVUS和MCU的所有病人。所有ceVUS均採用Philips Affiniti 70超聲系統進行。SonoVue被用作ceVUS的造影劑，然後所有病人再以碘化造影劑在螢光透視儀下接受MCU。我們在病人完成檢查後5天內進行後續電話訪談。

結果：共納入22名病人，包括18名男性和4名女性（年齡介乎19天至24個月）。總共檢查44個腎盂輸尿管單位（PUU）。在44個PUU中，有4個檢測到VUR。除了一個PUU在ceVUS上顯示為2級VUR而在MCU上顯示為1級VUR外，其他PUU在兩次檢查的結果皆一致。因此，若撇除兩種檢查在評估VUR重度上的差異，本研究顯示ceVUS對於VUR的檢測達到100%的敏感性和100%的特異性。其他發現包括腎積水（n=10）、輸尿管囊腫（n=1）、腎臟多囊性發育不良（n=1）、腎囊腫（n=1）和尿道憩室（n=1）。所有病人對檢查的耐受性良好，亦無明顯併發症。

結論：ceVUS準確和安全，並容許一站式結構和功能評估。我們以ceVUS檢測到的尿道憩室獨特病例也擴展我們對ceVUS於檢測尿道病變的認識。

INTRODUCTION

Diagnosis and grading of vesicoureteric reflux (VUR) are commonly performed using fluoroscopic examination micturating cystourethrogram (MCU) or radionuclide cystography.[1] Both of these techniques involve the use of ionising radiation, which is a significant concern in paediatric population. In the late 1990s, with the advent of contrast-enhanced voiding urosonography (ceVUS), VUR could be effectively diagnosed with a diagnostic accuracy higher than conventional modalities.[2-4] Joint imaging recommendations have been established by European Society of Paediatric Radiology and European Society of Urogenital Radiology.[5] ceVUS is also described in the European Federation of Societies for Ultrasound in Medicine and Biology clinical practice guidelines for contrast-enhanced ultrasound.[6]

In the US, sulphur hexafluoride lipid-type A microspheres (Lumason; Bracco Diagnostics Inc., Monroe Township [NJ], US), marketed elsewhere as SonoVue (Bracco Suisse, Geneva, Switzerland), received approval from the US Food and Drug Administration for ceVUS in paediatric patients in late 2016.[7] The value of ceVUS is acknowledged in American College of Radiology Appropriateness Criteria; however, there is not yet an established recommendation specific to ceVUS in the evaluation of childhood urinary tract infection (UTI).[8]

Earlier studies on ceVUS mainly used first-generation ultrasound contrast agent Levovist (Bayer-Schering, Berlin, Germany). However, with the withdrawal of Levovist in 2011, second-generation ultrasound contrast agent SonoVue has been used for ceVUS. A growing body of literature has rigorously assessed the safety and utility of SonoVue ceVUS. SonoVue ceVUS offers greater sensitivity than Levovist ceVUS of 80% to 100%.[3,9,10] Furthermore, it is more cost-effective, because the contrast dose requirement is lower[10] and the improved microbubble stability period of up to 6 hours allows multiple examinations to be performed after the vial of ultrasound contrast agent has been unsealed.[11]

Our centre was the second hospital in Hong Kong to introduce ceVUS, in August 2016. Since then, we have been performing both ceVUS and MCU in the same setting for each patient in order to monitor diagnostic

performance. The specific aim of the present study was to compare the diagnostic performance of ceVUS in our setting using MCU as a local conventional standard of practice for comparison. Furthermore, the safety profile of ceVUS was evaluated and relevant imaging findings described.

METHODS

We performed an institutional review board–approved retrospective review of all consecutive patients who underwent both ceVUS and MCU in the same setting performed in Department of Radiology, Pamela Youde Nethersole Eastern Hospital, between August 2016 and May 2017 inclusive. All patients scheduled for reflux imaging within the study period were included. Patients were referred by paediatricians owing to first episode of febrile UTI with associated risk factors in accordance with established local guidelines,[12] recurrent UTI, postnatal persistent hydronephrosis, and multicystic dysplastic kidney. A total of 22 patients (18 males, 4 females) were included, giving a total of 44 pelvi-ureteric units (PUUs) examined. The age range of the patients was from 19 days to 24 months on the day of examination. The clinical indications of the examination were as follows: UTI (n=15), postnatal persistent hydronephrosis (n=5), duplex kidney (n=1), and multicystic dysplastic kidney (n=1). All the patients received prophylactic antibiotics with oral trimethoprim at 2 mg/kg daily, 1 day prior to the examination and continued thereafter until paediatrics clinic follow-up.

Imaging Technique

All 22 patients first underwent ceVUS immediately followed by MCU. They received transurethral catheterisation using 5-Fr infant feeding catheter under aseptic technique for subsequent infusion of normal saline and contrast agents. A three-way stopcock was connected to the catheter; the remaining two hubs of the three-way stopcock were connected to an infusion set for normal saline and a syringe for injection of SonoVue. ceVUS examinations were performed using Philips Affiniti 70 ultrasound system (Philips Medical Systems, Nederland B.V., The Netherlands) with a C9-2 convex paediatric abdominal transducer (2-9 MHz). A preliminary greyscale ultrasound of the urinary system was performed for anatomical assessment and documentation of any abnormality such as hydronephrosis. Baseline scanning of bilateral kidneys and urinary bladder in contrast-specific harmonic imaging mode was then performed to identify any hyperechoic region before injection of SonoVue. The urinary bladder was instilled with normal saline via the urethral catheter until 30% of maximum bladder volume was reached. The age-specific bladder volume could be estimated by the formula: bladder capacity volume (mL) = [age (years) + 2] × 30 mL.[13] This was followed by an injection of 0.8 mL to 1.2 mL SonoVue at approximately 1% concentration. Saline infusion was continued until the patient began to void. Alternate transabdominal scanning of bilateral kidneys and urinary bladder using contrast-specific harmonic imaging mode was performed to detect any echogenicity from microbubbles in the PUU to suggest VUR. Interscrotal transperineal scanning was performed during micturition to image the urethra. The scanning was then repeated for a total of three voiding cycles with cyclic filling of normal saline after each voiding and in most cases without the need for additional SonoVue injection. We adopted cyclic filling because VUR is more readily disclosed with this approach.[14,15] In subsequent scanning cycles after each voiding, the intravesical microbubbles became progressively less concentrated than in preceding scanning cycles; this is beneficial for the detection of low-grade VUR in the distal ureters which could otherwise be easily obscured by the intense posterior shadowing from the relatively concentrated intravesical microbubbles in the initial scanning cycle.[16] Representative static ultrasound images and video loops were stored in the Patient Archiving and Communication System.

After the findings of ceVUS were documented, the patient was transferred to the fluoroscopic unit for MCU. All MCU examinations were done with an AXIOM Luminos TF fluoroscopy system (Siemens AG Medical Solutions, Forchheim, Germany). Via the same urethral catheter, iodinated contrast medium Conray 30 (Mallinckrodt Pharmaceuticals, Quebec, Canada) was infused into the bladder. Intermittent fluoroscopic screening of pelvic region during bladder filling and voiding phases was performed to detect any abnormal contrast opacification of the PUU to suggest VUR. The patient was put in left anterior oblique and right anterior oblique positions during MCU with one voiding cycle examined in each position, giving a total of two voiding cycles examined for each patient. The findings of MCU were then documented. Representative fluorograb images were acquired and stored in the Patient Archiving and Communication System.

Grading of Vesicoureteric Reflux

We followed the five-tier grading system for severity of VUR in ceVUS which is based on the International

Reflux Grading System traditionally applied on MCU (Table 1[17,18]).

Post-examination Assessment

All 22 patients were allowed to rest for 30 minutes after each examination to observe any adverse reaction after the procedures. On post-examination day 3 to day 5, the patients' parents or guardians were contacted via telephone to follow up on any signs or symptoms of complications. They were specifically asked about any pain or crying during voiding, haematuria, cloudy urine, foul-smelling urine, fever, retention of urine, or rash.

RESULTS

VUR was detected in four (9.1%) out of the 44 PUUs. One PUU showed grade 2 VUR on ceVUS but grade 1 VUR on MCU; all other PUUs show concordant findings in both examinations. Of the other refluxing PUUs, one was a duplex collecting system with grade 5 VUR to the lower moiety (Figures 1 to 5), one showed grade 4 VUR, and one other showed grade 2 VUR (Figures 6 and 7).

All refluxing PUUs detected on MCU were also detected on ceVUS; accuracy of detection of VUR was high, with sensitivity and specificity both reaching 100%. There was also high agreement of VUR grading between the two modalities (Table 2).

In addition to functional evaluation for VUR, other anatomical findings were detected, including hydronephrosis (n=10; one of these hydronephrotic PUUs being the refluxing duplex collecting system), ureterocoele (n=1) [Figures 8 and 9], multicystic dysplastic kidney (n=1), renal cysts (n=3), and urethral diverticulum (n=1) [Figure 10]. Except for the refluxing duplex collecting system, none of the other corresponding PUUs showed VUR on either ceVUS or MCU. The case of urethral diverticulum was only detectable on ceVUS

Table 1. Grading of vesicoureteric reflux in contrast-enhanced voiding urosonography.[17,18]

Grade 1	Microbubbles only in the ureter
Grade 2	Microbubbles in the renal pelvis; no significant renal pelvic dilatation
Grade 3	Microbubbles in the renal pelvis with significant renal pelvic dilatation and moderate calyceal dilatation
Grade 4	Microbubbles in the renal pelvis with significant renal pelvic dilatation and significant calyceal dilatation
Grade 5	Microbubbles in the renal pelvis with significant renal pelvic and calyceal dilatation, loss of renal pelvis contour and dilated tortuous ureter

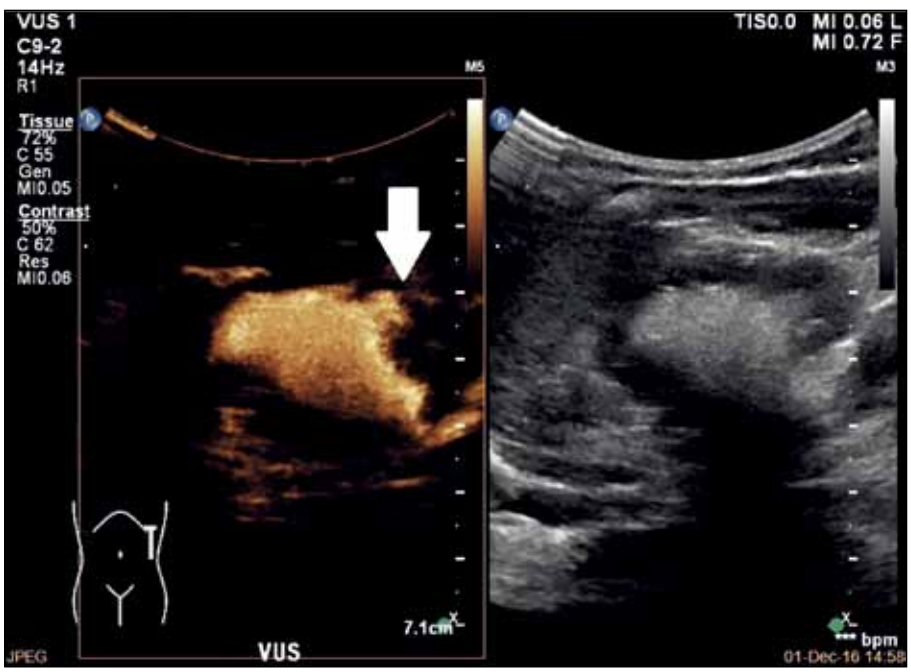

Figure 1. Patient A. Longitudinal contrast-enhanced voiding urosonography scanning over the left renal region. Contrast-specific harmonic imaging (left) and fundamental greyscale imaging (right) showing highly echogenic microbubbles present within dilated lower moiety pelvicalyceal system with blunting of renal calyces (white arrow), suggesting grade 5 vesicoureteric reflux.

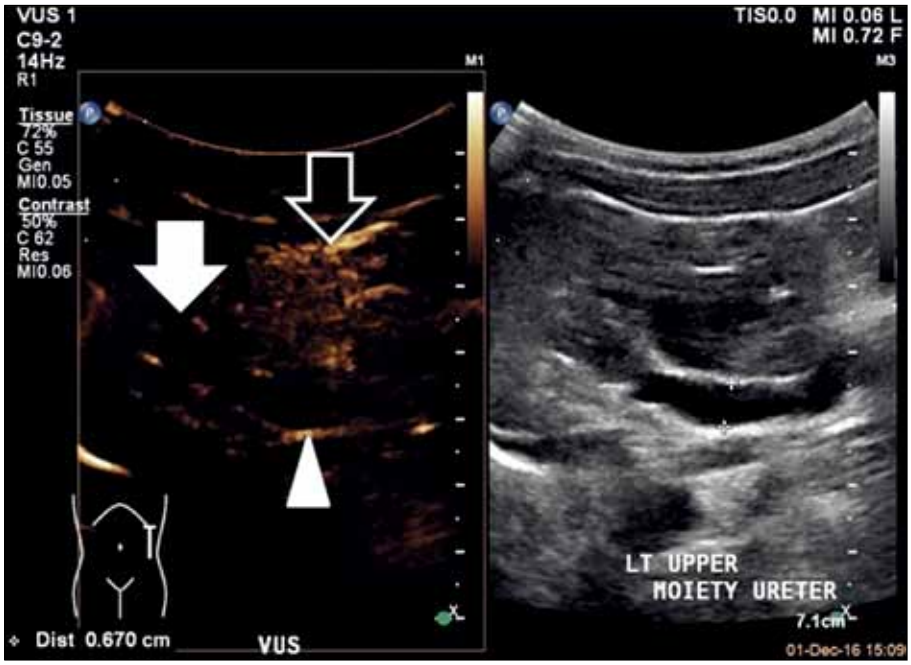

Figure 2. Patient A. Longitudinal contrast-enhanced voiding urosonography scanning over the left renal region focusing over the upper moiety of the duplex left kidney. Contrast-specific harmonic imaging (left) and fundamental greyscale imaging (right) showing no evidence of abnormal echogenicity within the dilated upper moiety pelvicalyceal system (white arrow) and upper moiety ureter (white arrowhead). Echogenic microbubbles are present within the lower moiety pelvicalyceal system (empty white arrow), suggestive of vesicoureteric reflux only in the lower moiety.

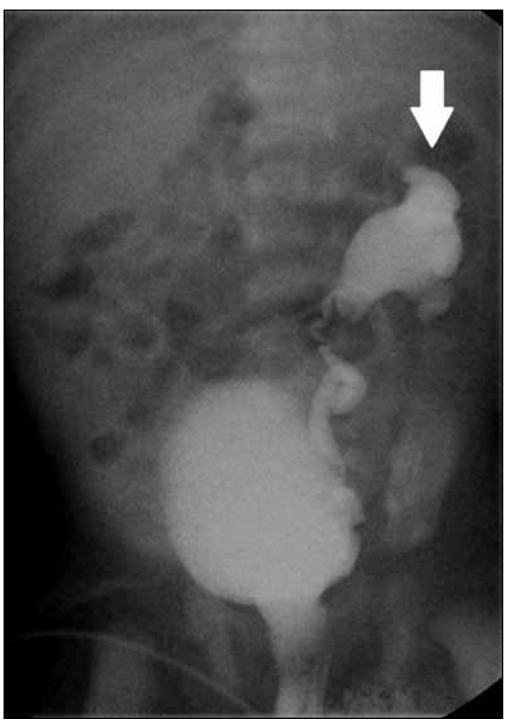

Figure 3. Patient A. Fluoroscopic image from micturating cystourethrogram examination showing reflux of iodinated contrast into the dilated left pelvicalyceal system with blunting of renal calyces (white arrow), suggesting grade 5 vesicoureteric reflux.

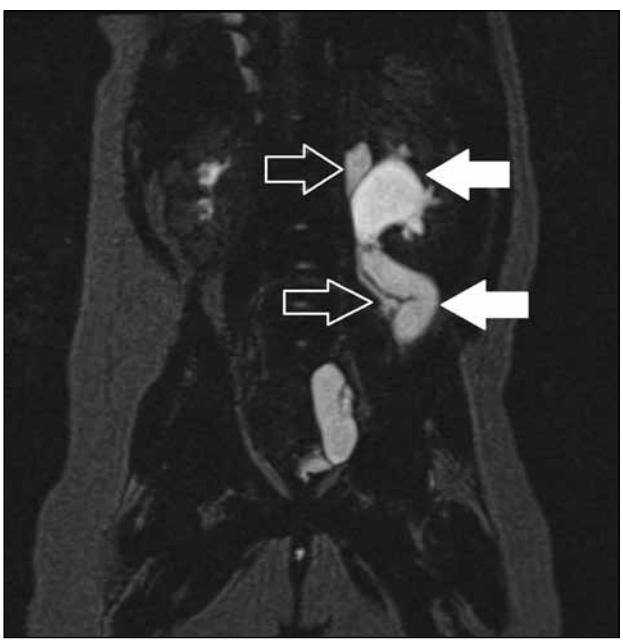

Figure 4. Patient A. Static coronal maximum intensity projection image of magnetic resonance urogram in T2-weighted turbo spin echo three-dimensional respiratory-triggered sequence showing the left duplex kidney with dilated pelvicalyceal system and ureters; the lower moiety renal pelvis and ureter are indicated by the white arrows while the upper moiety renal pelvis and ureter are indicated by the empty white arrows.

as a 5-mm outpouching in at the anterior aspect of the prostatic urethra; this finding was not detectable on MCU.

All 22 patients tolerated the examinations well, with no complications reported immediately after or up to 5 days after the examination.

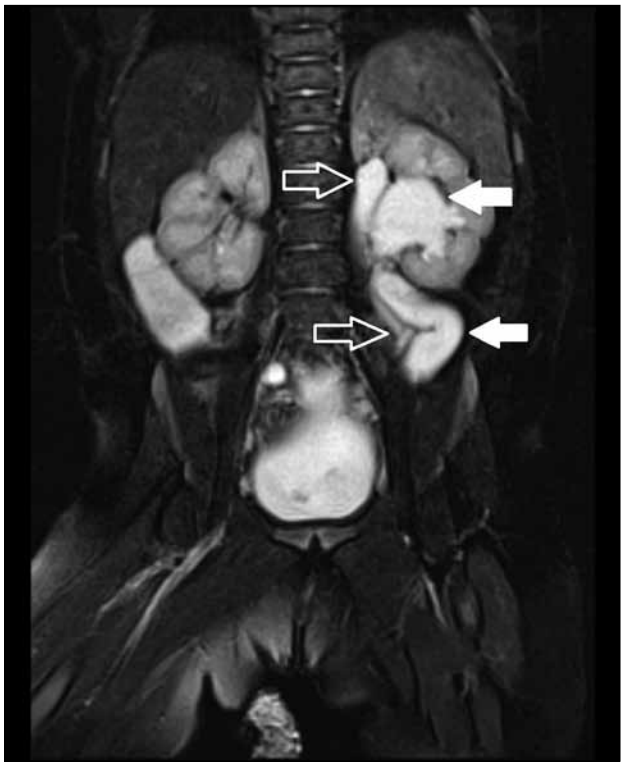

Figure 5. Patient A. Static coronal magnetic resonance urogram image in fat-suppressed T2-weighted turbo spin echo sequence showing the left duplex kidney with dilated pelvicalyceal system and ureters; the lower moiety renal pelvis and ureter are indicated by the white arrows while the upper moiety renal pelvis and ureter are indicated by the empty white arrows.

DISCUSSION

Conventional modalities for assessing VUR such as MCU or radionuclide cystography have intrinsic drawbacks of exposing paediatric patients to ionising radiation. Since the introduction of ceVUS to our hospital, we have been evaluating its diagnostic performance and safety profile in our setting. We also compare findings of ceVUS with those of MCU in a single appointment, and we have a relatively long post-examination follow-up of up to 5 days after the examination.

We found excellent agreement in the detection of VUR between ceVUS and MCU. This is consistent with results from other larger-scale studies,[3,9,10] including a prior study in Hong Kong population by Wong et al[19] that suggested the high diagnostic accuracy of ceVUS. The incidence of VUR was relatively low at 9.1% in our patients; this might have obscured the true diagnostic accuracy. However, this low incidence also suggests that many of our patients could have been spared from the radiation exposure from MCU, further substantiating the role of ceVUS in paediatric patients at relatively low risk of VUR.[20] ceVUS can also serve as a radiation-free assessment for subsequent follow-up in patients with VUR, given the additional benefit of reducing their radiation exposure from repeated MCU examinations. The mean entrance surface dose to patients with or

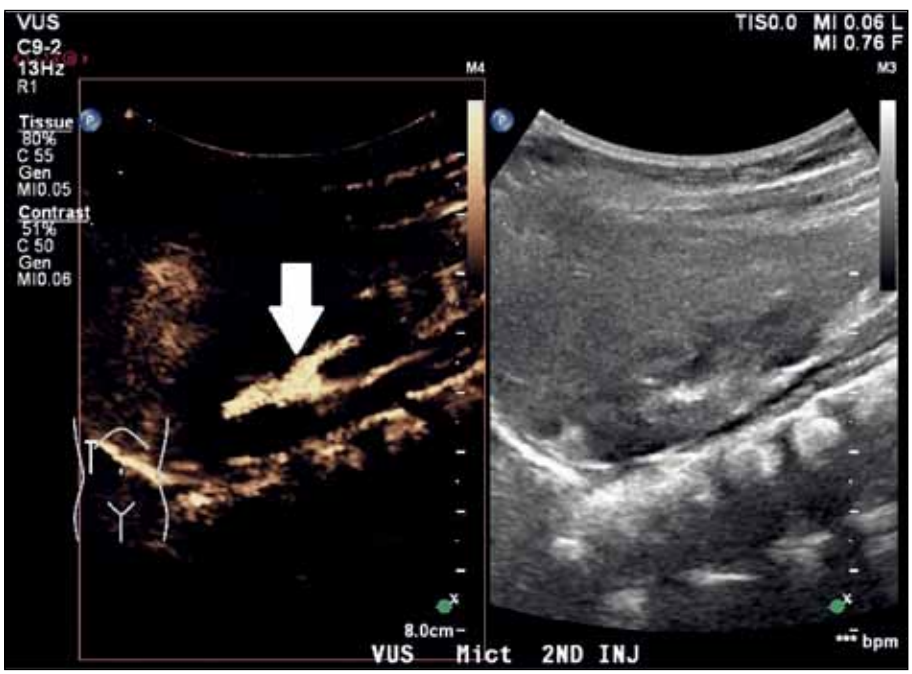

Figure 6. Patient B. Longitudinal contrast-enhanced voiding urosonography scanning over the right renal region. Contrast-specific harmonic imaging (left) and fundamental greyscale imaging (right) showing highly echogenic microbubbles present within non-dilated pelvicalyceal system (white arrow), suggesting grade 2 vesicoureteric reflux.

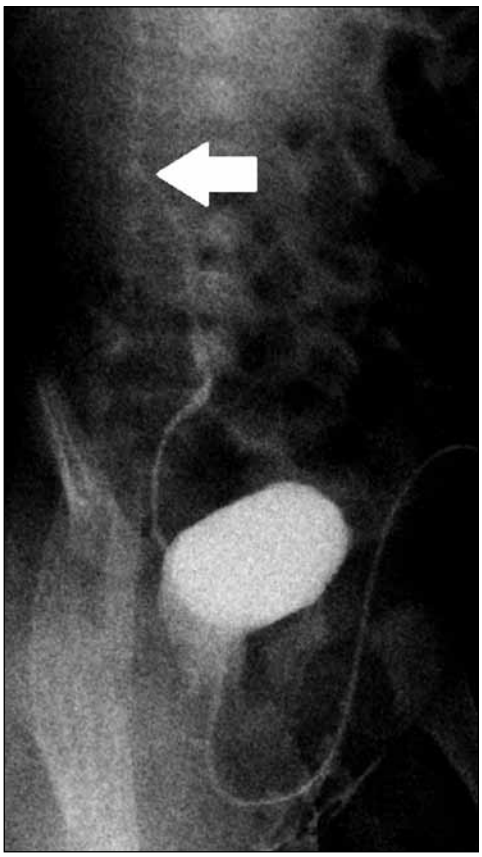

Figure 7. Patient B. Fluoroscopic image from micturating cystourethrogram examination showing reflux of iodinated contrast into non-dilated right pelvicalyceal system (white arrow), suggesting grade 2 vesicoureteric reflux.

Table 2. Results of contrast-enhanced voiding urosonography compared with micturating cystourethrogram.

Concordant results	No VUR	Grade 1 VUR	Grade 2 VUR	Grade 3 VUR	Grade 4 VUR	Grade 5 VUR
No VUR	40					
Grade 1 VUR			1			
Grade 2 VUR			1			
Grade 3 VUR						
Grade 4 VUR					1	
Grade 5 VUR						1

Abbreviation: VUR = vesicoureteric reflux.

without positive MCU findings has been estimated as 1.45 mGy or 1.05 mGy, respectively; and the estimated risks of malignancy to ovaries and testes were 4.4×10^{-7} and 3.3×10^{-7}, respectively.[21] Although these risks are low, cumulative radiation exposure is inevitable in patients with VUR requiring repeated follow-up MCU examinations.

Discordance between Contrast-enhanced Voiding Urosonography and Micturating Cystourethrogram

In the present study, one of the PUUs demonstrated grade 2 VUR in ceVUS but grade 1 VUR in MCU. This likely reflects a well-described phenomenon that ceVUS can detect higher-grade VUR not revealed on MCU.[10,18,22] Up to 62% of VUR can be diagnosed with

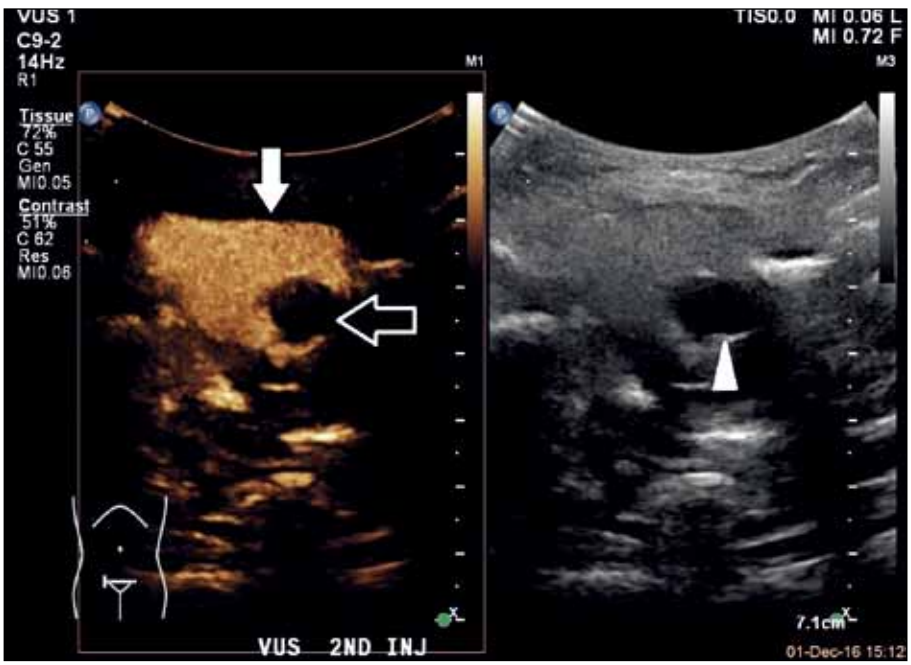

Figure 8. Patient C. Transverse contrast-enhanced voiding urosonography scanning over the suprapubic region. Contrast-specific harmonic imaging (left) and fundamental greyscale imaging (right) showing highly echogenic microbubbles infused into the urinary bladder (white arrow) during examination, outlining a roundish filling defect in left posterior aspect of urinary bladder which represents ureterocoele (empty white arrow), corresponding to the anechoic cystic structure on the greyscale image (white arrowhead).

ceVUS compared with up to 12% detected with MCU alone.[23] Various reasons have been proposed to account for this. Firstly, ceVUS allows more frequent imaging assessment, owing to the lack of radiation exposure, thus increasing the diagnostic yield for VUR. Secondly, a dilated PUU provides excellent anechoic background for detection of even miniscule amounts of highly reflective microbubbles, whereas dilution of iodinated contrast together with superimposed bowel shadows may lead to undetected higher-grade VUR in MCU, resulting in more false negative results in MCU than in ceVUS.[24] Furthermore, the intermittent nature of VUR itself likely contributes to the discordant findings between the two examination modalities, although it does not explain the skewed finding of higher-grade VUR detected in ceVUS. Conversely, ceVUS tends to miss lower-grade VUR more often than MCU; the probable reason behind is related to the obscuration of distal ureters by the highly echogenic microbubbles within the urinary bladder.[16] In our experience, we found that cyclic voiding helps to visualise the distal ureters more clearly. We adopted this scanning routine in ceVUS and this might have contributed to the excellent detection of VUR with ceVUS even in cases of low-grade VUR. The apparent discordance between ceVUS and MCU reflects the limitations of these examinations. Although neither examination is perfect, ceVUS allows the detection of more VUR than does MCU.

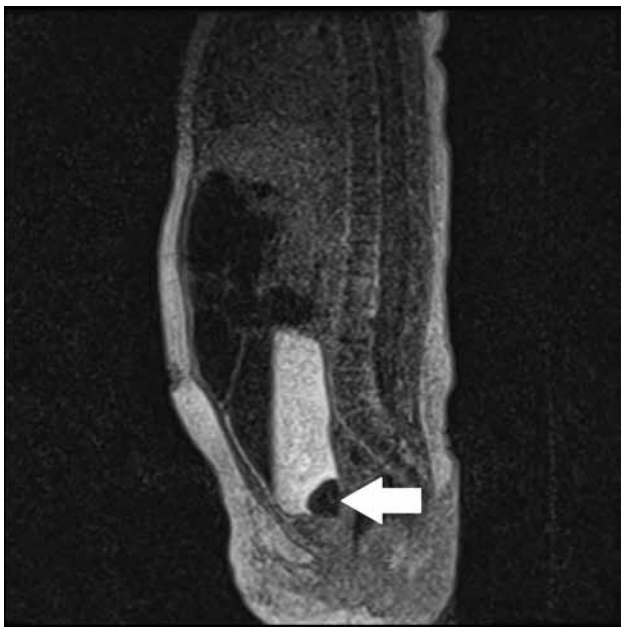

Figure 9. Patient C. Static sagittal image of magnetic resonance urogram in delayed phase gadolinium contrast-enhanced T1-weighted fat-suppressed sequence showing excreted gadolinium contrast in the urinary bladder with ureterocoele (white arrow) appearing as an oval-shaped filling defect in urinary bladder base.

Detection of Urethral Pathologies in Contrast-enhanced Voiding Urosonography

An important incidental finding was a case of urethral diverticulum in the prostatic urethra that was detectable on ceVUS but not on MCU. The small size of the diverticulum is a possible reason for obscuration in

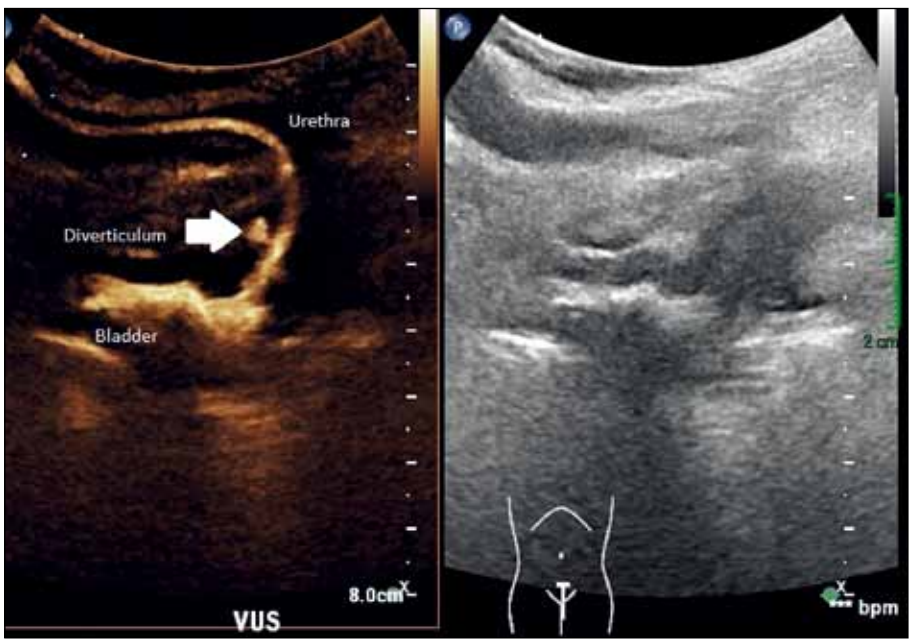

Figure 10. Patient D. Longitudinal contrast-enhanced voiding urosonography with transperineal interscrotal scanning during voiding. Contrast-specific harmonic imaging (left) and fundamental greyscale imaging (right) showing highly echogenic microbubbles passing from urinary bladder into urethra during voiding. A 5-mm contrast-filled outpouching at the anterior aspect of the prostatic urethra represents prostatic urethral diverticulum (white arrow) with normal calibre of the anterior and posterior urethra, suggesting absence of urinary flow obstruction.

MCU, as the visualisation of the posterior urethra during micturition is often impaired by artefacts from contamination of the surrounding area by the voided contrast. In the past, when interscrotal transperineal scanning approach of ceVUS was still not widely practised, experts maintained that MCU had a superior quality in assessment of male urethral pathologies.[25,26] However, later studies showed that transperineal scanning in ceVUS could allow excellent delineation of male urethral pathologies.[27-32] Our case of prostatic urethral diverticulum supports these studies by suggesting that ceVUS can detect more subtle pathologies of the male urethra than can MCU. Most major studies that have partially or specifically compared detection of urethral pathologies by ceVUS with that by MCU had a relatively limited range of diagnosis, including posterior urethral valves or, less commonly, anterior urethral valve and urethral stenosis. Other urethral pathologies, including urethral diverticulum, were not reported in the present study. To the best of our knowledge, there is only one reported case of diverticulum of prostatic utricle detected on ceVUS, as described in a more recent study by Duran et al.[33] Our case of prostatic urethral diverticulum is unique, and furthers knowledge of the potential of ceVUS in the detection of subtle urethral pathologies.

Safety of SonoVue Contrast-enhanced Voiding Urosonography

Our results showed an excellent safety record of ceVUS, with no complications encountered immediately and up to day 5 after the procedure. No complications related to catheterisation, infection, allergy, or adverse reactions to SonoVue were encountered. Although SonoVue has not yet been licensed for clinical application in infants and children, it has gained widespread off-label use, especially in Europe. A European questionnaire-based survey on SonoVue use in a paediatric population revealed that no adverse effects were encountered in 4131 children who received SonoVue ceVUS.[34] Eight prior major studies on the intravesical use of SonoVue for ceVUS, including one large-scale prospective investigation of SonoVue safety with 1010 study subjects,[35] reported no serious adverse events.[3,9,10,19,23,35-37] However, it remains unclear whether SonoVue has any long-term adverse effects; further research is required.

Limitations

Our results showed high diagnostic agreement between ceVUS and MCU. However, several limitations needed to be addressed. Firstly, the retrospective nature of our study and small sample size are substantial limitations. There was a relatively low incidence of VUR in the present study, which might hinder clear assessment of the diagnostic accuracy of ceVUS and MCU. Secondly, the lack of blinding of the operators from the results of ceVUS and MCU was also an important limitation. This could have led to biased interpretation of MCU findings due to preceding ceVUS results; however, the effect may not be significant as all patients were examined in a standardised MCU protocol. Despite these limitations, our findings can serve as local data for monitoring of diagnostic accuracy and service quality, as well as being a reference for other local or regional hospitals contemplating introduction of ceVUS.

ceVUS is a safe and effective tool for the detection of VUR with accuracy comparable to that of MCU without subjecting patients to ionising radiation, which is especially important for paediatric patients. ceVUS also allows one-stop functional and anatomical evaluation, which is not feasible with MCU alone. Earlier studies have challenged the quality of ceVUS in assessing urethral pathologies; however, our unique case of urethral diverticulum presents a counter-argument for this. Future prospective studies are needed to validate these preliminary observations. Our findings can serve as important local data for monitoring of diagnostic accuracy and service quality. Paediatric radiologists and clinicians should familiarise themselves with this new imaging alternative and incorporate it into their practice.

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