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# The learning curve of contrast-enhanced 'microbubble' voiding urosonography—validation study

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## Summary

### Introduction
Vesicoureteral reflux (VUR) is a common pediatric urologic condition associated with urinary tract infection and pyelonephritis. It can be diagnosed via fluoroscopic voiding cystourethrogram (VCUG) and, more recently, contrast-enhanced voiding ultrasonography (ceVUS), which does not expose the patient to ionizing radiation. Voiding urosonography contrast agents used for the diagnosis of VUR have been widely available in Europe but were approved by the Food and Drug Administration for use in the United States only in 2016.

### Objective
The objective was to optimize a protocol and compare the diagnostic performance of ceVUS to fluoroscopic VCUG in an academic medical center naïve to previous use of contrast-enhanced voiding urosonography.

### Study design
Thirty-nine patients referred for clinically indicated evaluation of VUR were enrolled between September 2016 and March 2017. Patients underwent contrast-enhanced ultrasonography with prediluted Lumason and under the same catheterization underwent fluoroscopic VCUG. Comparative grading was performed by pediatric radiologists on-site at the time of examination.

### Results
Reflux was observed in 16 of 39 patients (20 of 64 renal units) ranging from grades 1 through 5. VCUG and ceVUS were concordant for detecting reflux in 10 of 39 patients (14 of 84 renal units) and excluding reflux in 23 of 39 patients (64 of 84 renal units) (Fig. 1). Using contrast enhanced voiding urosonography, 1 of 20 renal units had high-grade and 2 of 20 renal units had low-grade reflux that was not found on fluoroscopy. Using fluoroscopy, 1 of 20 renal units had high-grade and 2 of 20 renal units had low-grade reflux that had not been found on ceVUS. Two of 20 renal units were upgraded from low-grade on ceVUS to high-grade on fluoroscopy. This corresponds to a Cohen's kappa of 0.72 (confidence interval [CI] 0.54—0.91) or 'moderate.'

### Discussion
During our investigation, we noted that there was a technical learning curve related to poor contrast mixing and the need to titrate the concentration of Lumason. However, over the course of the study, we were able to correct the technical aspects. Ultimately, our results showed good correlation between VCUG and Lumason ceVUS and only slightly less correlation than published studies by experienced centers. Future studies with voiding should allow for improved urethral visualization.

### Conclusion
While there is a considerable learning curve to the implementation of ceVUS for the diagnosis of pediatric VUR, these technical aspects can be corrected. Even a center previously naïve to contrast-enhanced ultrasound technology can, over a short period of time, demonstrate good correlation between VCUG and ceVUS in the diagnosis of VUR. Translation of ceVUS into clinical practice is an alternative to VCUG for diagnosis of reflux, is feasible, and can eliminate the radiation exposure associated with a VCUG.

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## Introduction

Vesicoureteral reflux (VUR) is a common pediatric urologic condition associated with pediatric urinary tract infection and can be associated with renal parenchymal damage in some cases [1]. Given the changing patterns of observation and treatment over the past several years, accurate diagnosis remains the cornerstone of its management. Contrast-enhanced voiding urosonography (ceVUS) was first introduced in the 1990s as a means of diagnosing VUR without the exposure to ionizing radiation inherent in fluoroscopic voiding cystourethrograms (fluoro VCUGs.) [2] (see Fig. 1). Commercial ultrasound contrast agents first became available in the 1980s; the current second-generation agents—with improved stability—were developed in 2001 [3]. However, owing to regulatory restrictions, their intravesical use has remained much more common in Europe than in the United States. A survey conducted by the European Section of Pediatric Radiologists documented over 5000 total examinations at 45 centers using the ultrasound contrast agent SonoVue® (Bracco, Milan, Italy) with over 4000 being ceVUS [4]. A 2009 survey of pediatric urologists who belonged to the American Academy Pediatrics Section on Urology, by contrast, noted that 98% preferred the use of fluoroscopic examination for evaluation of reflux despite being aware of the risks of radiation exposure [5].

Based on the combined results of four prospective clinical trials (Hong Kong, Slovenia, Hungary, and Greece) and review of 12 retrospective studies, intravesical sulfur hexafluoride (Lumason®, Bracco, Milan, Italy) was approved by the United States Food and Drug Administration (FDA) in December 2016 for the diagnosis of VUR in children [6]. It is currently the only contrast-enhanced ultrasound agent approved in the United States for this indication, but the same compound, under the name SonoVue®, remains the most commonly used contrast agent in Europe [7]. Validation studies were therefore conducted at institutions that, according to their published clinical trial data, had significant experience—in some cases with up to 20 years—using ceVUS prior to conducting prospective clinical trials comparing ceVUS to fluoroscopic VCUG [1]. Some studies claim that in experienced hands, ceVUS outperforms fluoroscopic VCUG in the diagnosis of reflux [8]. However, fluoroscopic VCUG remains the current gold standard for its well-validated ability to assess urethral and voiding pathology as well as VUR. The slope of the learning curve for pediatric urologists, sonographers, and radiologists adapting to this new technique remains undefined.

As such, the objectives of our study were twofold: first, to compare the diagnostic performance of ceVUS to fluoroscopic VCUG in our patient population, with radiologists, urologists, and ultrasonographers naïve to the use of ceVUS in the diagnosis of VUR and second, to optimize a protocol of contrast concentration, position, and ultrasound settings for ideal visualization of VUR via ceVUS.

## Materials and methods

This study was approved by the Stanford Institutional Review Board. From September 2016 to March 2017, 39 patients referred by pediatric urology for clinically indicated VCUG were enrolled. Patients were excluded at parental refusal or at the discretion of the referring pediatric urologist, with subjective criteria including known parent or child anxiety and previous intolerance of VCUG.

The patient was pretreated as per the institution's standard protocol with at least 24 h of therapeutically dosed oral antibiotic, and on the day of examination, the parent and patient were interviewed for the presence or absence of symptoms suspicious for urinary tract infection. There were no catheter-associated urinary tract infections diagnosed during or after the study. A commercially obtained contrast agent (Lumason) was mixed at the time of the examination, and both ultrasonic and fluoroscopic examinations were conducted in the same examination room under a single catheterization. There was no patient charge for ceVUS in this research study. Lumason is readily available through our pharmacy formulary. We do not anticipate cost or availability of contrast to be a limiting factor in the future. Subsequent to the study, we have implemented a

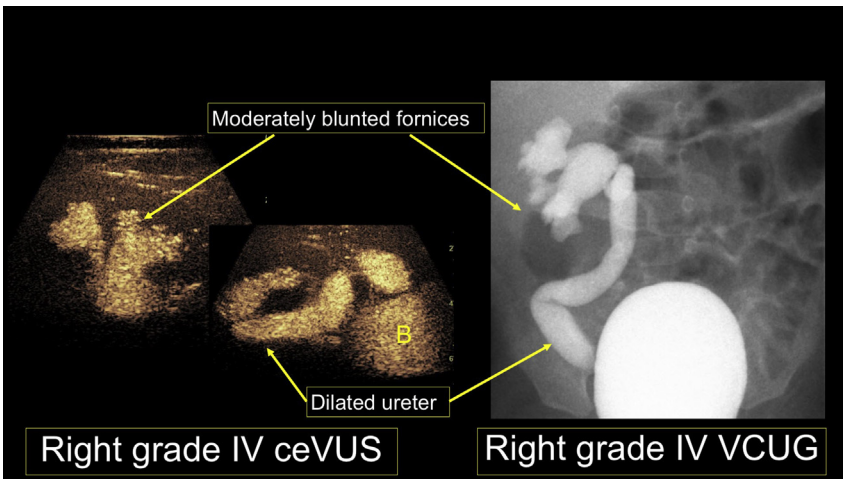


**Fig. 1** Grade 4 vesicoureteral reflux demonstrated on both contrast-enhanced ultrasound (left) and fluoroscopic VCUG (right). Bladder (B). VCUG, voiding cystourethrogram.

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clinical protocol for contrast ceVUS, and our charge is the same as a fluoroscopic VCUG.

We administered our contrast premixed by diluting the contrast in 250 ml IV bags of saline. We initially used 1 ml of contrast prediluted in 250 ml of saline, to a concentration of 0.4% contrast, similar to previous studies performed using the second-generation ultrasound agent Optison [9]. A study by Duran et al. [10], published after the initiation of this study, also suggested this premixing method in order to homogenize the contrast. However, during the initial two studies, we found that at this concentration, there was nonvisualization of posterior structures because of acoustic attenuation of the contrast. Following this observation, we diluted the contrast to a concentration of 0.1 ml in 250 ml saline (0.04%) for the patients who were followed up.

Two experienced ultrasound radiology techs acquired images for all examinations. Two attending pediatric radiologists with over 50 years of combined ultrasound experience provided oversight for the performance and interpretation of all examinations. Bladder catherization technique and filling of the bladder were performed according to the American College of Radiology and Society for Pediatric Radiology practice parameters for the performance of voiding cystourography in children [11]. Enrolled patients were catheterized by the pediatric radiologist utilizing an aseptic technique with the patient in the supine position. A pediatric feeding tube appropriate for patient size (5F or 8F) was placed and then secured to the dorsal aspect of the penis for boys and the thigh for girls. No sedation was administered for any of these patients. The bladder was emptied as completely as possible to minimize potential layering (unopacified) urine in the dependent portion of the bladder, and a urine culture was taken. We then obtained precontrast ultrasound images of both kidneys and the bladder. The purpose of the precontrast imaging was twofold: first, to assess for preexisting hydronephrosis and second, to optimize contrast technical settings on the ultrasound machine prior to introducing contrast. Optimization included selection of the best transducer frequency based on the patient's age and size. We then filled the bladder either to spontaneous micturition, desire for micturition, or patient agitation. When age-appropriate, the patient was then instructed to void with the catheter in place. Cyclic cine images of the bladder, each kidney, and bladder/urethra were obtained using a GE LOGIQ E9 ultrasound machine with C2-9, and/or 9L probes during filling and attempted voiding, with dual-mode greyscale and contrast imaging visualization. Initial imaging was performed during early filling of the bladder in the transverse and sagittal planes to assess for adequate mixing of contrast and detection of reflux into the distal ureters. Subsequent imaging of both kidneys in the transverse and longitudinal planes assessed for reflux into the kidneys and/or proximal ureters. Bladder and kidney imaging was continued by the ultrasound technician until either voiding occurred or there was maximum distention of the bladder resulting in patient discomfort. Urethral imaging was obtained suprapubically or transperineally based on what was deemed to be the best visualization window. If the patient was unable to void or residual urine remained in the bladder after voiding with the catheter in place, the bladder was then emptied via the existing catheter.

**Table 1** Patient demographics.

| Patient demographics | |
|---|---|
| Number of patients, n | 39 |
| Age, mean (+/− SD), months | 31.9 (38.7) |
| Age range (months) | 0—131 mo |
| Male gender, n (%) | 20 (51) |
| Indication, n | |
| Antenatal hydronephrosis | 12 |
| Febrile UTI with hydronephrosis | 12 |
| Febrile UTI without hydronephrosis | 8 |
| Neurogenic bladder | 3 |
| Other | 4 |
| Known non-hydronephrosis renal anomaly, n (%) | 10 (26) |
| Initial (primary) study, n (%) | 27 (69) |
| Imaging demographics | |
| Number of patients evaluated, n | 39 |
| Number of renal units evaluated, n | 83 |
| Poor contrast mixing during ultrasound, n (%) | 5 (13) |
| Poor image quality during ultrasound, n (%) | 6 (15) |
| Urethra evaluated on ultrasound, n (%) | 25 (64) |
| Urethra seen well on evaluation, n (%) | 15 (60) |
| Patient unable to void during ultrasound, n (%) | 5 (13) |

SD, standard deviation.
*Renal units: fully duplex kidneys considered 2 units; non-duplex kidneys considered 1 unit.

We then infused Cysto-Conray II (Liebel-Flarsheim, North Carolina, USA) through the existing catheter and performed a standard fluoroscopic VCUG using intermittent image capture fluoroscopy. The bladder was filled until discomfort or spontaneous voiding, at which time the catheter was removed and the patient was instructed to void to completion. If the patient was unable to void on table, the patient voided in the restroom immediately adjacent to the fluoroscopy suite and returned for fluoroscopy to assess for reflux. Final grading was performed using the International Reflux Study in Children, (ISRC), 1—5 scale by one of the two board-certified pediatric radiologists and 1 pediatric radiology fellow, who were on-site at the time of the examination [12]. Statistical analysis was performed using SAS® 9.4.

## Results

Thirty-nine patients ranging in age from 0 to 131 months were enrolled in the study. Eighty-four renal units were evaluated. A fully duplex kidney with separate ureters to the upper and lower poles was considered 2 units and non-duplex kidneys were considered one unit. Patient demographics, clinical indications for VCUG, and characteristics of imaging are listed in Table 1.

### Reflux vs no reflux

Of 39 patients (84 renal units), we observed reflux in 16 patients (20 renal units) ranging from grades 1 through 5. Three of 16 patients had bilateral reflux (Table 2). Three of

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**Table 2** Reflux vs no reflux (patients/renal units).

| Reflux vs no reflux on ceVUS and Fluoroscopic VCUG | Reflux on fluoroscopy | No reflux on fluoroscopy |
|---|---|---|
| Reflux on ceVUS | 10/14 | 3/3 |
| No reflux on ceVUS | 3/3 | 23/64 |

CK — patients: 0.6538, CI 0.40—0.91.
CK — renal units: 0.7781, CI 0.61—0.95.
Renal units: fully duplex kidneys considered 2 units; non-duplex kidneys considered 1 unit.
CI, confidence interval; CK, Cohen's kappa coefficient.

**Table 3** High-grade (grade 3 or higher reflux) vs low-grade (grade 2 or lower reflux) vs absent reflux (renal units).

| Comparison of Reflux Grade for ceVUS and Fluoroscopy VCUG | High-grade on fluoro | Low-grade on fluoro | Absent on fluoro |
|---|---|---|---|
| High-grade on ceVUS | 9 | 0 | 1 |
| Low-grade on ceVUS | 2 | 3 | 2 |
| Absent on ceVUS | 1 | 2 | 64 |

CK: 0.721, SE 0.0937, 95% CI 0.5378—0.905.
CI, confidence interval; CK, Cohen's kappa coefficient; SE, standard error.

16 patients were found to have reflux on fluoroscopy only, and 3 of 16 were found to have reflux on ceVUS only. On fluoroscopy, reflux occurred during the filling phase in 9 of 16 patients and only during voiding in 4 of 6 patients. During ceVUS, reflux occurred during filling in 12 of 16 patients and only during voiding in 1 of 16 patients. All 'discordant' patients (patients who demonstrated reflux on one modality but not the other) had unilateral reflux. If fluoroscopic VCUG is considered a gold standard, traditional sensitivity of ceVUS is 77% and specificity is 88%. However, this assumes that a positive ceVUS in the setting of a negative VCUG is a false positive.

### High- vs low-grade reflux

Patients were divided into high- and low-grade groups based on their ISRC grade—high grade being grades 3—5 and low grade being grades 1—2. This differentiation between high grade and low grade is for ease of clinical interpretation, due to the decreased likelihood of spontaneous resolution and increased likelihood of sequelae such as renal scarring or need for surgery in patients with high-grade reflux. Using ceVUS, 1 of 20 renal units had high-grade reflux and 2 of 20 renal units had low-grade reflux that was not found on fluoroscopy (Table 3). No renal units were upgraded from low grade on fluoroscopy to high grade on ceVUS. Using fluoroscopy, 1 of 20 renal units were found to have high-grade reflux and 2 of 20 renal units were found to have low-grade reflux that was not found on ceVUS; however, this was seen only during the fluoroscopic voiding phase after catheter removal. Two of 20 renal units were upgraded from low grade on ceVUS to high grade on fluoroscopy.

On a Cohen's test of interrater reliability (comparing fluoroscopic VCUG to ceVUS without considering either of them the gold standard), the level of agreement between fluoroscopic VCUG and ceVUS is 'moderate' for both individual patients with/without reflux and renal units by high grade/low grade of reflux. Owing to the high proportion of negative studies, concordance measured by Cohen's kappa was higher among renal units than individual patients.

## Discussion

The recent FDA approval of a sulfur hexafluoride contrast agent in the United States under the trade name Lumason opens new avenues for the radiation-free diagnosis of VUR in the United States. Our study represents the first implementation of Lumason ceVUS in an academic setting naïve to the technology. Two attending pediatric radiologists provided oversight for the performance and interpretation of examinations for the study. The initial learning curve for study interpretation was largely dependent on optimizing technical factors to assure consistent high-quality images. Subsequently, ceVUS has been introduced into clinical practice with a very fast learning curve. All pediatric radiologists in the department have become comfortable with performing the studies after observing and performing two to four examinations. The diagnostic performance, as described in our results section, demonstrated 77% sensitivity and 88% specificity if fluoro VCUG is considered the gold standard. It also demonstrated a statistically significant Cohen's interrater reliability score of 0.65 ('moderate') for reflux/no reflux and 0.72 ('moderate') for high-grade vs low-grade vs no reflux diagnosed via fluoro VCUG vs ceVUS. We would suggest that sensitivity/specificity, while it is well understood by clinicians, may not be the appropriate measure and may even be misleading: while a ceVUS that does not demonstrate reflux in the setting of a VCUG that does is likely to be a false negative (affecting sensitivity), a ceVUS that demonstrates reflux in the setting of a VCUG that does not is unlikely to be a false positive (affecting specificity.) Other studies in experienced centers have demonstrated a Cohen's kappa of up to 0.77 by a renal unit, which is consistent with our findings, with up to 0.91 ('excellent') with the use of contrast-enhanced color Doppler voiding urosonography [13].

Notably, our methods included having the patient void around the existing catheter at the conclusion of ceVUS to prevent a second catheterization for VCUG. While physiologically voiding around the catheter should have been possible [14], practically speaking 13% were documented as being unable to void at all with the catheter in place at the conclusion of ceVUS. Furthermore, the patient's bladder was filled to fussy behavior or feeling of micturition, and not to calculated bladder capacity; this may have underestimated the proportion of patients with reflux, especially with low-grade reflux. Patients were encouraged to void with the catheter in place; however, if the patient demonstrated fussiness or discomfort, the bladder was emptied through the existing catheter whether they were able to void, due to our protocol requiring a subsequent fluoroscopic VCUG.

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Two patients later diagnosed with reflux during VCUG were unable to void at the conclusion of ceVUS with the catheter in place, including one with grade 3 reflux detected fluoroscopically with voiding after catheter removal. Small amounts of urine passing around the catheter without a significant urine stream may also have been associated with Valsalva voiding or lack of full bladder contraction, including in one patient who was upgraded from grade 2 at ceVUS to 4 at fluoro VCUG. One occasion of upgrade from low grade on ceVUS to high grade on fluoroscopy was associated with incomplete bladder filling during ceVUS—when filled to capacity during VCUG, the reflux was upgraded to high grade.

There was a considerable technical learning curve in the identification of the optimal concentration, position, and ultrasound settings for ideal visualization of VUR. First, the SonoVue studies documented in the Lumason FDA approval utilized a technique of instilling 1 ml of non-diluted Lumason directly into a partially full bladder. One milliliter of Lumason in a 30-ml newborn bladder would represent a concentration of 3%, markedly more dense than the manufacturer's recommended concentration. The concentration of premixed contrast that we ultimately used was significantly less dense than even the manufacturer's recommended concentration—anything more dense caused acoustic attenuation of posterior structures. This practice of premixing contrast also aided in consistency of visualization—the visualized microbubble density was the same, regardless of bladder size and capacity, which would not have been the case otherwise.

Furthermore, in 13% of our studies, we found poor contrast mixing at the time of ultrasound. We noted that even contrast that had been previously diluted would layer with the small amount of urine that remained in the dependent portion in the bladder, which could potentially produce a false negative result. This false negative effect was observed in previous studies, noting that residual fluoroscopic contrast at the time of ultrasound contrast instillation would efface the appearance of microbubbles on ultrasound [15]. Duran et al. [10] described that this contrast-urine level produced by residual urine would eventually disappear with a full bladder and allow visualization of posterior structures, but this was not always our experience.

While a detailed discussion of the individual ultrasound settings and probes is outside this scope, it is important to note that despite the extensive experience of our ultrasonographers, 15% of our patients were documented as having poor image quality on ultrasound, which were attributable to technical factors that were later optimized. We also noted the importance of precontrast imaging of the kidneys, bladder, and urethra to optimize technical factors prior to introducing contrast. We ultimately decided to use transperineal imaging rather than suprapubic imaging in the majority of cases for optimal visualization of the urethra. We also noted the advantage of ceVUS over fluoroscopy for detection of a small number of refluxing bubbles, especially in the case of pre-existing hydronephrosis, as compared to the contrast dilution that can occur in the setting of fluoroscopic examination. However, we also observed the importance of real-time imaging to distinguish between reflux and other normal motions of the body, such as bowel peristalsis. Wozniak et al. [16] also documented the importance of real-time imaging in voiding urosonography, especially as, unlike in fluoroscopic VCUG, the entire system cannot be visualized at one time [10].

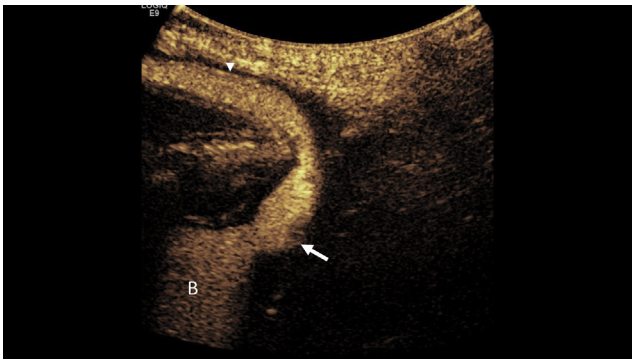


**Fig. 2** Transperineal image of urethra. Good visualization of urethra demonstrated during voiding on contrast-enhanced ultrasound. Bladder (B), posterior urethra (arrow), anterior urethra (arrowhead).

Overall, the concordance between fluoro VCUG and ceVUS was high, but our study has several limitations. Notably, some patients did not void during the ultrasonographic study, although they were all able to void during fluoroscopic VCUG once the catheter was removed. This potentially results in false negatives on ceVUS, when reflux occurred only during voiding. Our study population, despite being small, was heterogenous, including one patient with a horseshoe kidney, one with a solitary kidney, one with renal dysplasia, one with multicystic dysplastic kidney, two with ureteroceles, and five with at least one duplex kidney. Of the 16 patients diagnosed with reflux, 9 were undergoing follow-up studies and had a history of previously known reflux on VCUG, which introduces potential bias as study graders were not blinded to outcomes of previous examinations. We also did not assess our intergrader reliability of ceVUS grading, but in studies at experienced centers, it has been documented to be as high as 100% [1].

While it was not a primary objective of the study, we were able to obtain excellent ultrasound visualization of the urethra in several patients (see Fig. 2). However, the urethra was only adequately observed in 64% of patients secondary to inability to adequately void around the catheter during the study. None of our study population had a known or previously suspected urethral abnormality. The role of ceVUS for evaluation of the male urethra has been described in previous studies from several high-volume and experienced centers [10,17,18]. We are planning to study urethral evaluation after catheter removal in future studies.

In summary, we found good correlation between VCUG and Lumason ceVUS on initial implementation and plan to continue the use of Lumason ceVUS at our institution as a primary method for the evaluation of VUR in patients without potential risk factors for urethral pathology. Further directions for studies include surveying the attitudes and acceptability of ceVUS among the institution's urology and nephrology providers after widespread implementation, assessing ceVUS grading using blinded

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reviewers, and assessing the use of ceVUS in videourodynamics.

## Author statements

### *Ethical approval*

This study was approved by the Stanford Institutional Review Board.

### *Funding*

None.

### *Competing interests*

None.

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