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Feasibility of Antegrade Contrast-enhanced US Nephrostograms to Evaluate Ureteral Patency¹

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Purpose:

To demonstrate the feasibility of contrast material-enhanced ultrasonographic (US) nephrostograms to assess ureteral patency after percutaneous nephrolithotomy (PCNL) in this proof-of-concept study.

Materials and Methods:

For this HIPAA-compliant, institutional review board-approved prospective blinded pilot study, patients undergoing PCNL provided consent to undergo contrast-enhanced US and fluoroscopic nephrostograms on postoperative day 1. For contrast-enhanced US, 1.5 mL of Optison (GE Healthcare, Oslo, Norway) microbubble contrast agent solution (perflutren protein-type A microspheres) was injected via the nephrostomy tube. Unobstructed antegrade ureteral flow was defined by the presence of contrast material in the bladder. Contrast-enhanced US results were compared against those of fluoroscopic nephrostograms for concordance.

Results:

Ten studies were performed in nine patients (four women, five men). Contrast-enhanced US demonstrated ureteral patency in eight studies and obstruction in two. One patient underwent two studies, one showing obstruction and the second showing patency. Concordance between US and fluoroscopic assessments of ureteral patency was evaluated by using a Clopper-Pearson exact binomial test. These results were perfectly concordant with fluoroscopic nephrostogram results, with a 95% confidence interval of 69.2% and 100%. No complications or adverse events related to contrast-enhanced US occurred.

Conclusion:

Contrast-enhanced US nephrostograms are simple to perform and are capable of demonstrating both patency and obstruction of the ureter. The perfect concordance with fluoroscopic results across 10 studies demonstrated here is not sufficient to establish diagnostic accuracy of this technique, but motivates further, larger scale investigation. If subsequent larger studies confirm these preliminary results, contrast-enhanced US may provide a safer, more convenient way to evaluate ureteral patency than fluoroscopy.

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Ultrasonography (US) is a powerful, portable imaging modality free of the risks of ionizing radiation and has a wide variety of diagnostic applications. However, conventional US has been found inadequate for evaluating ureteral patency even when used to assess urine jets at the ureteral orifices (1). The addition of microbubble US contrast agents to conventional US has substantially expanded the repertoire of US, enabling more sensitive and specific diagnosis by facilitating dynamic real-time assessment of the vascularity in visceral organs, with excellent spatial and contrast resolution (2). The excellent safety profile of US microbubble contrast agents is equal or superior to that of computed tomography (CT) or magnetic resonance (MR) contrast agents with regard to serious adverse events (3). Although contrast material-enhanced (CE) US has been in widespread clinical use for decades outside of the United States (2), we found no report of it being used to assess antegrade ureteral patency.

Since the microbubbles used as US contrast agents remain within the vascular system and are not excreted into the collecting system, evaluation of ureteral patency with CE US requires the contrast agent to be instilled directly into the renal collecting system. An important population of such patients are those who undergo percutaneous nephrolithotomy (PCNL) for treatment of kidney stones (4). PCNL is the standard treatment for renal stones larger than 2 cm (5). A fluoroscopic nephrostogram, the imaging reference standard to assess ureteral patency, is often performed the day following PCNL through an indwelling nephrostomy

tube to inform the decision to remove the nephrostomy tube (6). Radiation dose reduction is of particular interest in patients with nephrolithiasis because they already have elevated radiation exposure related to diagnostic and intra-procedural imaging (7).

The purpose of this proof-of-concept study is to demonstrate the feasibility of CE US nephrostogram to assess ureteral patency after PCNL.

Materials and Methods

Study Design

This study was compliant with Health Insurance Portability and Accountability Act and approved by the institutional review board. Adult patients undergoing PCNL at our medical center were recruited for participation in this prospective study from September 2015 through October 2015. Patients were excluded if they declined informed consent or had contraindication to intravascular US contrast agents (8) (even though this study did not involve intravascular use of contrast agents). Additionally, patients were excluded if fluoroscopic dose was not available or if staff was not available to perform the US study (eg, weekends). At our institution, fluoroscopic nephrostograms and conventional US are performed as part of routine clinical care in all patients following PCNL; however, the CE US portion of the examination was performed as research.

All study subjects underwent PCNL and had a Foley bladder catheter as well as either a 10-F Cope loop catheter (Cook Medical, Bloomington, Indiana) or a 16-F Foley catheter (Bard Medical, Covington, Georgia) percutaneous nephrostomy tube left in place after the procedure. The nephrostomy tube was capped

on the morning of postoperative day 1 after PCNL as part of normal clinical practice. On postoperative day 1, both CE US and fluoroscopic nephrostograms were performed within 2 hours of each other. In anticipation of CE US, the bladder drainage catheter was clamped 2 hours prior to scanning to achieve a mildly distended urinary bladder for better visualization of the US microbubble contrast agent. In four of the 10 studies, the CE US portion was performed prior to fluoroscopic nephrostogram. In the six other studies, the fluoroscopic nephrostogram was performed prior to CE US.

For CE US studies, the initial conventional gray-scale US was performed by sonographers. The CE portion of the examination was performed and interpreted by one of either two attending radiologists (S.W. and J.M.) with 5 and 10 years, respectively, of abdominal US subspecialty training. A GE LOGIQ E9 (GE Healthcare, Chicago, Ill) system was used with a C1-6 curved-array transducer. Off-label usage of US contrast agent in the renal collecting system was approved by the institutional review board. A dose of 1.5 mL of US contrast agent solution (Optison, perflutren protein-type A microspheres injectable suspension; GE Healthcare, Oslo, Norway) was injected via the existing nephrostomy tube, followed by a 5 mL normal saline flush. Since no prior data on the

Advances in Knowledge

- Use of microbubble contrast agents instilled through a nephrostomy tube enables evaluation of ureteral patency with US.
- Ten contrast-enhanced US nephrostograms in nine patients demonstrated 100% concordance with fluoroscopic nephrostograms.

Implication for Patient Care

- If large-scale trials confirm diagnostic accuracy, contrast-enhanced US nephrostograms will allow for evaluation of ureteral patency without exposing patients to ionizing radiation.

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Abbreviations:

CE = contrast material enhanced
PCNL = percutaneous nephrolithotomy

Author contributions:

Guarantors of integrity of entire study, T.C., M.U., M.P.K., S.W.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, T.C., M.U., P.J., H.C.C., S.W.; clinical studies, all authors; experimental studies, T.C., M.U., S.W.; statistical analysis, T.C., M.U., J.M., P.J., S.W.; and manuscript editing, T.C., M.U., J.M., M.P.K., A.T., P.J., H.C.C., S.W.

Conflicts of interest are listed at the end of this article.

appropriate dosing for nephrostograms were available, we used a slightly increased dose relative to what would be used in an intravenous CE study to mitigate contrast agent strength dilution from pre-existing urine in the collecting system. A Luer lock type syringe (Becton Dickinson, Franklin, NJ) and three-way stopcock were used to facilitate injection and prevent spillage of the solution. Initial focused US of the kidney with the nephrostomy tube was performed of the renal collecting system, including the renal pelvis and the visualized ureter, and of the bladder looking for residual stones, hydronephrosis, and to establish a baseline for visual evaluation for enhancement. The scan was then repeated immediately after injection of the contrast agent, evaluating the collecting system to ensure that contrast agent was successfully instilled and the ureter to determine level of any obstruction in the visualized portion. The time at which contrast agent was first visualized in the bladder was recorded. The GE LOGIQ E9 (GE Healthcare) system was used with the same C1-6 curved-array transducer. CE US was performed by using harmonic real-time imaging at low mechanical index of 0.05–0.10. Cine loop images were recorded, documenting the presence or absence of the contrast agent in the collecting system and bladder. The study was terminated when the contrast agent became obviously present in the bladder. If the contrast agent was not seen in the bladder after 5 minutes, a repeat 1.5 mL contrast agent injection and 5 mL saline flush was performed. If after 10 minutes no contrast agent was seen in the bladder, the study was terminated and the ureter was considered obstructed. This timing was determined to maintain consistency between the timing of re-injection and for allowing ample time for the contrast agent to pass in partially obstructing or slow flowing systems. This timing would be analogous to typical times for fluoroscopic nephrostograms to observe ureteral patency once the contrast agent is injected. During and for 4 hours after imaging, the patient was closely monitored for possible adverse reactions from the contrast agent injection.

In our study, we applied several techniques for optimizing the performance of CE US based partly on previously published experiences in abdominal imaging (8). To avoid breaking of the US contrast agent microbubbles, a large 18-gauge needle was used for drawing up the contrast agent solution. We also used a three-way stopcock to connect the syringes containing the contrast agent and normal saline flush to the nephrostomy tube. This facilitated contrast agent administration and minimized spillage. High pressure during injection will burst the microbubbles (9), so we administered the contrast agent with gentle pressure for more than 30 seconds. Two types of nephrostomy tubes are commonly used at our institution, a 10-F Cope loop catheter and 16-F Foley catheter. For injection into the latter, the stopcock was connected to a Christmas tree connector. These techniques helped preserve the integrity of the US contrast agent and facilitated collecting system injection.

Traditional fluoroscopic nephrostogram was also performed on the same day (within 2 hours) as the CE US. One of either two interventional radiologists (M.K. and A.T.), each with more than 5 years of experience, performed and interpreted the nephrostograms. They were blinded to the US results for those cases where US was initially performed prior. The patient was placed supine on the fluoroscopy table. Initial plain-film radiography was performed and then 10 mL of contrast agent solution (iohexol, Omnipaque; GE Healthcare, Chicago, Ill) was injected via the nephrostomy tube. Multiple fluoroscopic images were obtained of the collecting system and ureters. Fluoroscopic screening time (in seconds) and estimated radiation exposure dose (milligray per centimeter squared) from the machine were recorded. We did not control for whether the CE US or the fluoroscopic nephrostogram was performed first. If an obstruction was encountered, the patient would be offered repeat evaluation on postoperative day 2 with repeat CE US and fluoroscopic nephrostography.

Statistical Analysis

Concordance between CE US and fluoroscopic assessments of ureteral patency was evaluated by using a Clopper-Pearson exact binomial test with a null hypothesis probability of .5. Confidence intervals were calculated. The statistical software used was NCSS version 11 (www.ncss.com).

Results

Eighteen PCNLs were performed during the recruitment period. Nine patients (five men and four women) were enrolled. One patient declined the study, five patients were not enrolled due to staff availability to perform research studies off hours, and three patients were excluded in the analysis because fluoroscopic doses were unavailable. A total of 10 studies were performed, with one patient undergoing a repeat study. Mean age was 49.5 years \pm 13.9 (range, 30–72 years) and mean body mass index was 32.6 kg/m² \pm 10.3 (range, 22.9–55.1 kg/m²) (Table 1). The degree of preexisting hydronephrosis prior to nephrolithotomy was noted, which ranged from none (seven patients), to mild (one patient), to severe (one patient).

On US images, the renal collecting system was well visualized in all studies after injection of 1.5 mL of US contrast agent (Fig 1). The contrast agent was seen in the bladder (Fig 2, Movie [online]) in eight studies, indicating ureteral patency. The time before contrast agent reached the bladder ranged from 20 seconds to 6 minutes 30 seconds. Two studies failed to demonstrate contrast material in the bladder at 10 minutes and therefore the system was considered obstructed (Table 2). One patient underwent a repeat US and fluoroscopic nephrostography on postoperative day 2, within 24 hours of the first examination.

For fluoroscopic nephrostograms, the mean fluoroscopic screening time and radiation exposure dose were 213.3 seconds \pm 324.0 (range, 24–1113 seconds) and 11319 mGy \cdot cm² \pm 18706 (range, 9–62258 mGy \cdot cm²), respectively (Table 2).

Table 1

Patient Characteristics and Preoperative Parameters

Parameter	Value
Mean age (y)	49.5 ± 13.9 (30–72)
No. of men*	5 (55.6)
No. of women*	4 (44.4)
Mean body mass index (kg/m ²)	32.6 ± 10.3 (22.9–55.1)
Mean preoperative serum creatinine (mg/dL)	1.12 ± 0.38 (0.74–1.77)
Mean preoperative hematocrit (%)	42.6 ± 6.2 (35.0–52.2)

Note.—Unless otherwise indicated data are means ± standard deviation, with range in parentheses.

* Data in parentheses are percentages.

Figure 1

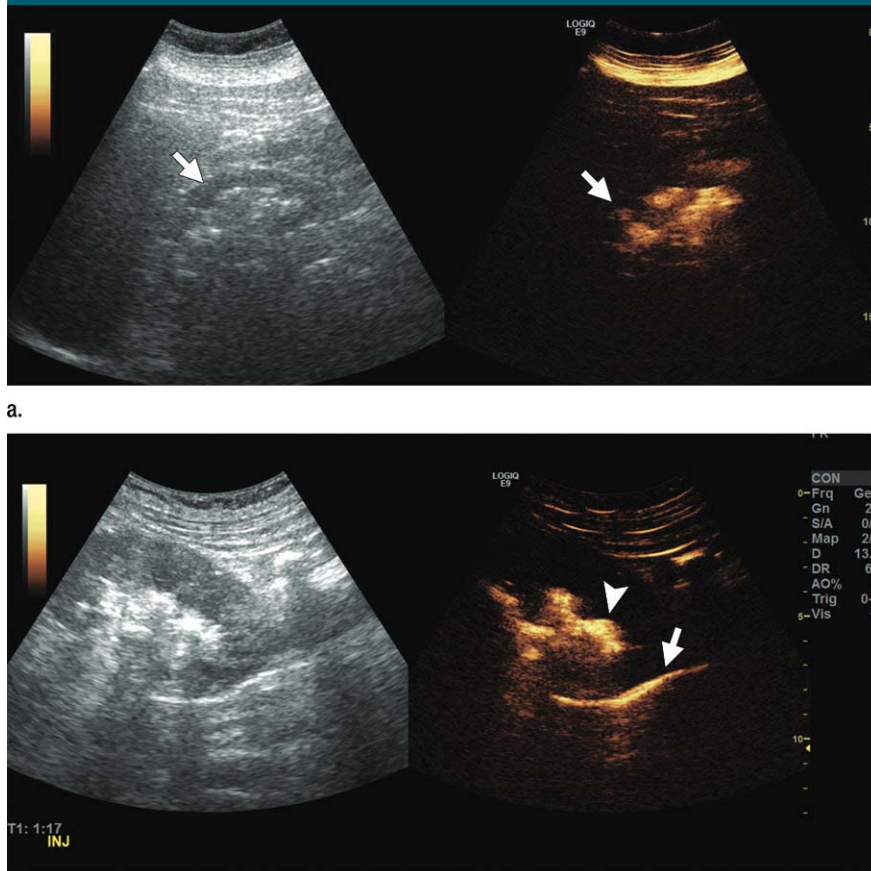


Figure 1: Dual-screen gray-scale (left) and CE (right) US images of the collecting system after contrast material injection via a nephrostomy tube in a 72-year-old man 1 day after PCNL. **(a)** Longitudinal views of the kidney with contrast material distributed throughout the renal collecting system (arrows). **(b)** Contrast material is distributed throughout the renal collecting system (arrowhead) and proximal ureter (arrow).

CE US assessment of obstruction was perfectly concordant with fluoroscopic assessment (10 of 10; 95% confidence interval: 69.2%, 100%). The null hypothesis of 50% agreement between CE US and fluoroscopy was

rejected ($P = .002$). There were no adverse events from US or iodinated contrast agent injection observed during any imaging study or 4-hour observation period.

For seven patients, initial CE US nephrostograms demonstrated patent ureters and their nephrostomy tubes were removed successfully immediately after imaging. For the other two patients, repeat CE US and fluoroscopic nephrostograms were offered on postoperative day 2. In the patient who underwent repeat imaging within 24 hours for an initially obstructed system, the repeat CE US and fluoroscopic nephrostogram (Fig 3) demonstrated unobstructed antegrade flow. This facilitated nephrostomy tube removal on day 2. Another patient declined the repeat CE US but fluoroscopic nephrostogram 24 hours after the first imaging was obtained. This showed ureteral patency and therefore the nephrostomy tube was removed after the study and the patient was subsequently discharged.

Discussion

This proof-of-concept investigation demonstrated that antegrade patency of the ureters can be evaluated by using CE US in patients with a nephrostomy tube present. Although the sample size of this pilot study was too small to confidently establish diagnostic accuracy, the perfect concordance of results with current standard-of-care fluoroscopic results is encouraging.

CE US in the urinary system has been widely studied in the evaluation and diagnosis of vesicoureteral reflux in pediatric patients. The safety of intravesical CE US in children has been shown with no major associated adverse effects (10), and a comparative study has shown CE US to have a diagnostic accuracy of 90% in comparison to voiding cystourethrography (11). Another application of intraluminal CE US, known as voiding urosonography, also shows potential for evaluating the urethra (12).

These emerging applications are promising from a radiation exposure reduction and patient safety standpoint.

Figure 2

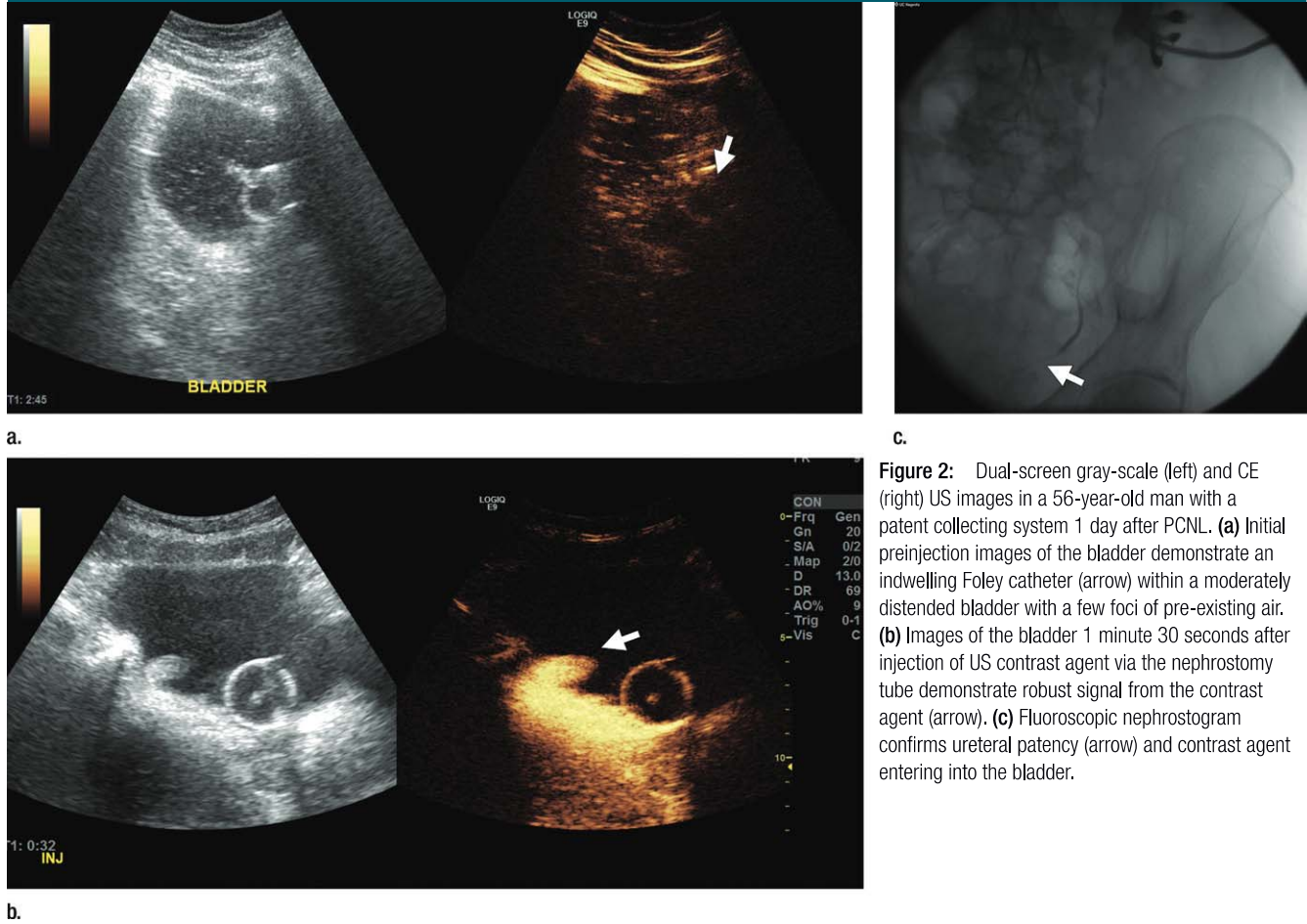


Figure 2: Dual-screen gray-scale (left) and CE (right) US images in a 56-year-old man with a patent collecting system 1 day after PCNL. **(a)** Initial preinjection images of the bladder demonstrate an indwelling Foley catheter (arrow) within a moderately distended bladder with a few foci of pre-existing air. **(b)** Images of the bladder 1 minute 30 seconds after injection of US contrast agent via the nephrostomy tube demonstrate robust signal from the contrast agent (arrow). **(c)** Fluoroscopic nephrostogram confirms ureteral patency (arrow) and contrast agent entering into the bladder.

Table 2

Study-specific Demographic, Procedural, and Imaging Characteristics

Sex/Age (y)/ Body Mass Index (kg/m ²)	Nephrostomy Laterality	Nephrostomy Tube Type	Preoperative Hydronephrosis	Contrast-enhanced US		Fluoroscopic Nephrostogram		
				Patent Ureter	Time until Contrast Agent is Seen in Bladder	Patent Ureter	Fluoroscopic Screening Time (sec)	Radiation Exposure Dose (mGy · cm ²)
M/30/23.6	Left	Cope loop	No	Study 1, no/repeat study 2, yes	Not applicable/ 2 minutes	No/yes	1113/72	62258/5000
M/72/33.7	Right	Cope loop	No	Yes	5 minutes	Yes	78	12
M/56/26.08	Left	Cope loop	No	Yes	1 minute 30 seconds	Yes	132	9
F/67/22.9	Left	Foley catheter	No	Yes	6 minutes 30 seconds	Yes	282	8000
F/56/41.1	Right	Cope loop	Severe	Yes	2 minutes	Yes	84	7054
F/46/26.3	Right	Foley catheter	Mild	Yes	30 seconds	Yes	24	3000
F/41/55.1	Left	Cope loop	No	Yes	20 seconds	Yes	60	10851
M/50/37	Left	Cope loop	No	Yes	1 minute	Yes	138	17000
M/47/36.1	Right	Cope loop	No	No	Not applicable	No	150	12

There have been no reports of serious adverse events related to urinary administration of US contrast agent.

Unlike the vascular system, the normal urinary system does not contain immune cells such as macrophages

and lymphocytes (13). Therefore, foreign material in the urinary system is unlikely to cause allergic reaction.

Figure 3

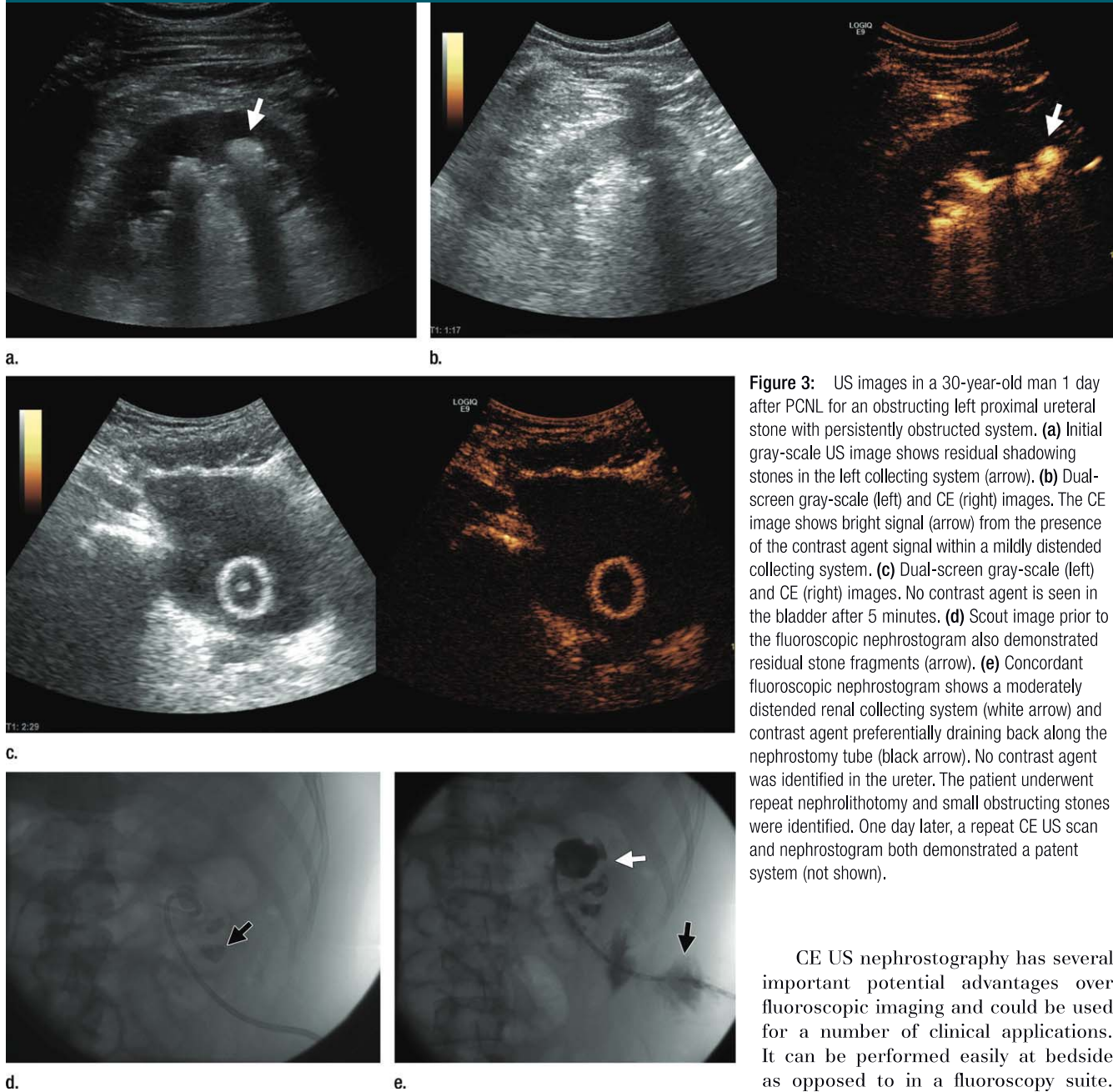


Figure 3: US images in a 30-year-old man 1 day after PCNL for an obstructing left proximal ureteral stone with persistently obstructed system. **(a)** Initial gray-scale US image shows residual shadowing stones in the left collecting system (arrow). **(b)** Dual-screen gray-scale (left) and CE (right) images. The CE image shows bright signal (arrow) from the presence of the contrast agent signal within a mildly distended collecting system. **(c)** Dual-screen gray-scale (left) and CE (right) images. No contrast agent is seen in the bladder after 5 minutes. **(d)** Scout image prior to the fluoroscopic nephrostogram also demonstrated residual stone fragments (arrow). **(e)** Concordant fluoroscopic nephrostogram shows a moderately distended renal collecting system (white arrow) and contrast agent preferentially draining back along the nephrostomy tube (black arrow). No contrast agent was identified in the ureter. The patient underwent repeat nephrolithotomy and small obstructing stones were identified. One day later, a repeat CE US scan and nephrostogram both demonstrated a patent system (not shown).

There is minimal to no entry into the vascular system with this type of injection, so the risks imposed by nephrostomy tube intraluminal administration should be substantially lower than with intravenous injection. A safety study of intravesical US contrast agent administration for diagnosis of vesicoureteral reflux in children reported no serious

adverse events (10). Minor events were reported in 3.6% of the pediatric study population, including dysuria, urinary retention, abdominal pain, blood, mucous discharge, and urinary tract infection. All of these were self-limited, did not require hospitalization, and were most likely related to the catheterization process (10).

CE US nephrostography has several important potential advantages over fluoroscopic imaging and could be used for a number of clinical applications. It can be performed easily at bedside as opposed to in a fluoroscopy suite. This allows for portable imaging, may improve patient care efficiency and access, and may decrease length of hospital stays if US scanners have more availability than fluoroscopy suites. The volume of contrast agent injected may also be lower for US compared with fluoroscopy, which may reduce the risk of over-distension of the collecting system when there is ureteral

obstruction. Finally, although the US contrast agent is typically more expensive per dose than iodinated contrast agent (\$80–\$140 vs \$5), CE US could still represent an overall less expensive imaging modality compared with fluoroscopy when taking into account the relative cost and the availability of a US scanner relative to a fluoroscopy suite. With its ability to detect ureteral obstruction, its application can be extended to evaluation of other causes of upper urinary tract obstruction, such as ureteropelvic junction obstruction and malignant ureteral obstruction.

This current study has several limitations. Although this investigation demonstrated 100% concordance with fluoroscopic results, there is a wide confidence interval range of 69% to 100% due to the small sample size. Larger studies are needed to narrow the width of the confidence interval. The confidence interval and the *P* value are approximate due to the possible correlation of results from the one patient with two examinations. Additionally, this study did not randomize the order in which CE US and fluoroscopic nephrostogram were performed. The mechanical effect of the volume of material injected in the first study could potentially have affected the ureteral patency for the second, though this should not have had a substantial effect on concordance between studies. An inherent limitation of US is that portions of the ureters are typically obscured by overlying bowel gas. Although CE US can depict obstruction in these cases based on absence of contrast agent in the bladder, it may provide less information about the level of obstruction than fluoroscopy, which is not limited by bowel gas. However, given the hyperechoic signal from the US contrast agent in the collecting system, visualization of the ureters is often better than experience with typical unenhanced gray-scale US would suggest.

Although this investigation involved only patients with unilateral nephrostomy tubes, the technique could be

extended to evaluate both ureters in a patient with bilateral nephrostomies. The challenge in a bilateral evaluation would be that the contrast agent injected into the first tube might obscure or be confused with the contrast agent coming from the second tube. To avoid this, there are several means by which the urinary system could be cleared of the contrast agent prior to the second injection: the renal collecting system could be flushed with saline, the bladder could be drained and re-irrigated, and any remaining microbubbles could be burst with high mechanical index pulse application. CE US may be limited in differentiating between a complete or incomplete ureteral obstruction. However, partial obstruction that does not substantially delay flow may not be clinically relevant.

In conclusion, this preliminary study demonstrates that CE US can be used to evaluate antegrade ureteral patency in patients with nephrostomy tubes and has potential advantages over fluoroscopy in terms of patient safety (including radiation exposure) and convenience. Larger scale studies will be powered to evaluate diagnostic accuracy of this technique relative to current standard of care.

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