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Applications of contrast-enhanced ultrasound in the pediatric abdomen

Aikaterini Ntoulia,[1] Sudha A. Anupindi,[1,2] Kassa Darge,[1,2] Susan J. Back[1,2]

[1]Department of Radiology, Children's Hospital of Philadelphia, 3401 Civic Center Boulevard, Philadelphia, PA 19104, USA
[2]Perelman School of Medicine, University of Pennsylvania, Philadelphia, USA

Abstract

Contrast-enhanced ultrasound (CEUS) is a radiation-free, safe, and in specific clinical settings, highly sensitive imaging modality. Over the recent decades, there is cumulating experience and a large volume of published safety and efficacy data on pediatric CEUS applications. Many of these applications have been directly translated from adults, while others are unique to the pediatric population. The most frequently reported intravenous abdominal applications of CEUS in children are the characterization of focal liver lesions, monitoring of solid abdominal tumor response to treatment, and the evaluation of intra-abdominal parenchymal injuries in selected cases of blunt abdominal trauma. The intravesical CEUS application, namely contrast-enhanced voiding urosonography (ceVUS), is a well-established, pediatric-specific imaging technique entailing the intravesical administration of ultrasound contrast agents for detection and grading of vesicoureteral reflux. In Europe, all pediatric CEUS applications remain off-label. In 2016, the United States Food and Drug Administration (FDA) approved the most commonly used worldwide second-generation ultrasound contrast SonoVue®/Lumason® for pediatric liver and intravesical applications, giving new impetus to pediatric CEUS worldwide.

Key words: Contrast-enhanced ultrasound—CEUS—Children—Pediatric population—Intravenous—Intravesical—Intracavitary—Applications—IV CEUS—ceVUS—Safety

Over the recent decades, the pediatric applications of contrast-enhanced ultrasonography (CEUS) have expanded [1–5]. Pediatric CEUS combines all of the advantages of ultrasonography performance in children with the real-time information of ultrasound (US) contrast agent's pharmacokinetics within tissues/organs.

Ultrasound contrast agents can be injected intravenously for the evaluation of the enhancement patterns of solid organs in various clinical settings or can be administered into the urinary bladder (intravesical) or other physiologic body cavities (intracavitary), such as the pleural space or other spaces in order to identify abnormal communication tracts [1]. Moreover, they are not nephrotoxic and, similar to adults, they have an overall favorable safety profile when administered in children with very low incidence of adverse events [4, 6–11]. Performance of CEUS does not involve the use of ionizing radiation, does not require any specific patient preparation or sedation, and does not need preliminary screening laboratory tests prior to contrast administration.

Currently, second-generation US contrast agents are available in the market. The most commonly used contrast agents are SonoVue® (Bracco, Milan, Italy) in Europe, and Optison™(General Electric Healthcare, USA), Definity® (Lantheus Medical Imaging, USA), and Lumason® (Bracco, Milan, Italy) in the United States. Lumason® is exactly the same contrast agent as the worldwide agent SonoVue® but is marketed in the United States under this different proprietary name.

For many years, none of these second-generation US contrast agents were licensed for use in children. However, this limitation did not preclude the performance of a variety of clinically indicated pediatric CEUS applications. Historically, most pediatric CEUS examinations were performed in Europe, with the off-label use of SonoVue® according to the guidelines and recommendations of the European Society of Pediatric Radiology as well as the European and World Federation of Societies for Ultrasound in Medicine and Biology, respectively,

Correspondence to: Aikaterini Ntoulia; *email:* ntouliaa@email.chop.edu

and in research settings by obtaining informed consent from the parents and/or children themselves if applicable, according to institutional policies [1, 12–14].

In the United States, due to a different regulatory framework, there has been more limited experience with pediatric intravenous and intravesical CEUS applications [15–20].

In 2016, the United States Food and Drug Administration (FDA), taking into consideration the large volume of published safety and efficacy data for SonoVue®/Lumason®, approved and subsequently revised the product labeling for its intravenous liver applications in adults and children as well as intravesical applications in children. This FDA approval of Lumason® gave new momentum to pediatric CEUS worldwide signifying its recognition as a valuable imaging tool in specific clinical settings thereby avoiding unnecessary radiation exposure particularly in children.

The aim of our review article is to describe the most common abdominal CEUS applications in children and highlight procedural and safety issues pertinent to the pediatric population.

Intravenous CEUS: dose and procedural considerations

The most frequently reported intravenous (IV) abdominal CEUS applications in children are the characterization of focal liver lesions, post-treatment monitoring of solid abdominal tumors, and the evaluation of intra-abdominal parenchymal injuries in selected patients with blunt abdominal trauma [1, 2, 7, 11, 21]. Other, constantly evolving IV CEUS applications include evaluation of liver and renal transplants, and monitoring of inflammatory bowel disease [22, 23].

When performing pediatric CEUS, several dose and technical factors need to be taken into account. The FDA approved dose for pediatric liver IV CEUS with Lumason®/SonoVue® is 0.03 mL/Kg up to a maximum of 2.4 mL per injection [24]. Before Lumason®/SonoVue® FDA approval, several dose schemes for intravenous applications were reported in pediatric literature depending on the child's age and weight as well as the intended application, as follows:

Recommended Lumason®/Sonovue® pediatric IV dosing based on the current literature

(a) 0.03 mL/Kg up to a maximum of 2.4 mL per injection [24];
(b) 0.6 mL for children younger than 6 years, 1.2 mL for children between 6 and 12 years old, and 2.4 mL for children older than 12 years old [9];
(c) 0.1 mL per year of age [25];
(d) 0.1 mL/Kg for children weighting up to 24 kg, and 2.4 mL for children weighting more than 24 kg [8];
(e) 0.4 ± 0.3 ml for children weighting less than 20 kg and 1.0 ± 0.4 ml for children weighting more than 20 kg [10]; and
(f) Arbitrarily selected standard doses of 0.1, 0.5, 1.2, 2.4, or 4.8 mL [6, 23, 26].

Regarding Optison™, the pediatric dosage scheme that has been proposed for IV administration is based on body weight.

Recommended Optison™ pediatric IV dosing based on the current literature

0.3 mL for children weighing less than 20 kg and 0.5–0.6 mL for children weighing more than 20 kg [15–18].

However, we need to point out that the dose of any US contrast agent depends on various parameters including the US contrast agent itself, the US equipment, and the contrast-specific software used. Therefore, the contrast dose should be adjusted, as needed, to optimize image quality.

The timing of the vascular phases for intravenous pediatric CEUS administration may be different from those in adults due to physiologic differences in blood circulation and the size of the IV catheter line, which can limit the injection rate. For these reasons, recording cinematic loops instead of acquiring static images alone starting immediately after the injection and lasting up to 5 min is important to allow for thorough post-procedure evaluations and quantitative analysis. In our experience, cinematic recording is most critical in the first minute, whereas static images can be obtained intermittently in the later 4 min. It is important to note that all the above-mentioned second-generation US contrast agents are pure blood pool agents and remain intravascular throughout all vascular phases; therefore, there is no interstitial enhancement phase. The enhancement pattern of a lesion reflects blood flow and is compared to that of the adjacent parenchyma.

Special emphasis should be given to the fact that lesions should be well visualized on baseline gray scale US in order to be further targeted for IV CEUS. The ultrasound settings, including gain, scanning depth, and time gain compensation should be optimized for each examined region independently before the examination. Low Mechanical Index (MI) should be used to prevent microsphere destruction. In all cases, IV bolus injection of US contrast agent should be followed by saline flush in order to push forward the small volume of US contrast agent through the IV and associated extension tubing into the blood circulation.

If a repeated dose is needed, residual US contrast agent should be cleared from blood circulation, either by its progressive decay until the baseline appearance of the

organ is again observed or by rapid decay using specific high MI techniques.

Intravenous CEUS: safety considerations

Similar to adults, IV administration of US contrast agents in children has an overall high safety profile. In 2015, a systematic literature review article was published summarizing safety data from the IV use of SonoVue® and Optison™ in children [7]. The data was extracted from 19 studies available in the literature, which were conducted between 2004 and 2015 and included a total of 502 children who underwent 655 IV CEUS examinations. Overall, 10 children experienced adverse reactions related to the IV use of US contrast agents: one severe and nine minor.

Piskunowicz et al. reported the one severe adverse event [6]. In this case, an 11-year-old girl had a life-threatening anaphylactic reaction that occurred immediately after IV contrast administration of SonoVue® and presented with generalized pruritus and nausea, hypotension, and initial tachycardia that turned to bradycardia. The reaction subsided 2 h later following treatment with oxygen, intravenous administration of epinephrine and fluids.

Four studies reported the remaining minor adverse events in nine children who underwent IV CEUS with SonoVue® or Optison™, including mild, self-limited headaches, altered taste, nausea, tinnitus, and light-headedness [17, 18, 27, 28]. It is important to mention that in one of these studies, three children who had initially experienced minor adverse events underwent a follow-up IV CEUS, and these symptoms did not re-occur in the subsequent examination [18].

Following the 2015 literature review article, four additional original studies were published and included pediatric safety data from the IV administration of SonoVue® and Optison™ [8–10, 15]. In these studies, a total of 546 new patients were included who underwent 665 IV CEUS examinations. Among them, one study reported 2 children who experienced mild adverse events related to the IV administration of the US contrast agent SonoVue®, which manifested as nausea and single cutaneous wheal [10]. However, after the completion of this study, an additional case of a severe adverse event due to SonoVue® administration occurred that was reported as an addendum to the study results [10]. This case referred to an 11-year-old girl who developed acute arterial hypotonia, flushing, emesis, and required short-term in-patient monitoring and treatment with steroids, antihistamines, and fluids.

Overall, to date, among the 1048 reported children who underwent 1320 IV CEUS examinations, 2 children experienced severe adverse events due to the IV use of US contrast agents and 11 experienced minor adverse events, accounting for 0.0015 and 0.008 of this cumulative population, respectively.

These findings highlight the importance that precautions should always be in place for managing possible adverse events and that IV administration of US contrast agents should only be performed by adequately trained medical personnel.

Intravenous CEUS: applications

Focal liver lesions

The most commonly reported application of pediatric IV CEUS is the characterization of focal liver lesions that are detected on baseline US and remain indeterminate in nature following gray scale and color Doppler examination [9, 10, 21, 26].

In routine practice, indeterminate liver lesions will require additional diagnostic investigations before a definitive diagnosis can be made. These additional investigations include one or often a combination of the following: laboratory workup, cross-sectional imaging with contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI), follow-up US, or biopsy/surgery. However, each of these additional approaches is associated with limitations/disadvantages, which need to be considered particularly in the pediatric population.

CT is associated with a significant ionizing radiation burden on the developing pediatric tissues and organs as well as with potential risks related to the administration of iodinated contrast media including severe allergic reactions, contrast-induced nephrotoxicity in the immature pediatric kidneys, and thyroid dysfunction due to excess iodine load [29–31].

On the other hand, MRI is radiation-free and undoubtedly is considered the imaging modality of choice for characterization of hepatic mass lesions. However, it is expensive, not readily available, requires longer examination times and also involves the administration of gadolinium-containing contrast media with the potential risks of nephrogenic systemic fibrosis and the yet unknown consequences of gadolinium tissue depositions [32, 33]. Moreover, performing CT or MRI in children often requires sedation/general anesthesia, which further add to the overall risks involved in children who undergo these diagnostic imaging examinations.

For these reasons, IV CEUS has been adopted by many centers as a problem-solving imaging modality that can positively contribute in this diagnostic algorithm and in many cases can provide an immediate definitive diagnosis, obviating the need for further investigation and reducing parental and patient anxiety [3].

Following intravenous administration of US contrast agents, real-time evaluation of the enhancement pattern of targeted liver lesions during contiguous vascular

phases can reveal tumor-specific blood flow patterns suggestive of the benign or malignant nature of the imaged lesion.

The most characteristic example in pediatric IV CEUS is focal nodular hyperplasia (FNH). This lesion often demonstrates nonspecific imaging features on baseline US that may mimic malignancy [34, 35]. FNH diagnosis is of particular importance in children with a prior history of treated malignancy since combined treatments with chemotherapy and/or radiation therapy can predispose these children to developing multifocal FNH [36]. After intravenous administration of US contrast agents, the rapid appearance of the typical spoke-wheel pattern in the arterial phase followed by iso- or hyper-enhancement of the lesion in the portal-venous and iso-enhancement in the delayed phase can establish with confidence a definite diagnosis (Fig. 1) [37, 38].

Similar high diagnostic results can be achieved in case of solitary infantile hepatic hemangiomas. Similar to other imaging modalities, IV CEUS demonstrates the characteristic progressive centripetal nodular enhancement pattern that eventually becomes iso-enhancing with the adjacent liver parenchyma (Fig. 2) [38]. The possibility of prolonged examination times, particularly in cases of large hepatic hemangiomas, to achieve a final diagnosis occurs without the risk of any additional radiation exposure or other procedural-related restrictions. However, in cases of multifocal or diffuse forms, IV CEUS may be technically difficult and unsuitable for the comprehensive examination of the entire liver parenchyma. In these cases, MRI is the appropriate imaging modality for the accurate evaluation of all lesions to determine the full disease burden and to guide further management [39].

Pediatric IV CEUS can also be used for the clarification of other benign lesions such as focal or diffuse fatty changes, cysts and hepatic adenomas (Fig. 3) [26]. The imaging features suggestive of the benign nature of a focal liver lesion is when its enhancement is iso-enhancing or hyper-enhancing to the normal liver parenchyma during the portal-venous and delayed phases [38].

Primary malignant liver lesions are rare in pediatric population accounting only for 1–4% of all childhood cancers [40]. Among them, the most commonly reported primary pediatric hepatic malignancies are hepatoblastomas, fibrolamellar carcinomas, epithelioid hemangioendotheliomas, hepatocellular carcinomas, and rarely hepatobiliary sarcomas [40]. Although IV CEUS may have lower diagnostic specificity, it is very sensitive to demonstrate the hallmark features of malignancy; the heterogeneous, disorganized enhancement pattern and the early wash-out with hypo-enhancement in the delayed phase compared to the adjacent liver parenchyma [41].

In addition, IV CEUS can improve the conspicuity of a lesion by improving visualization of its internal composition (solid, cystic or mixed components), delineating its margins and evaluating the local invasiveness. Another important application of IV CEUS is monitoring of treatment response in non-surgical candidates with solid abdominal tumors. Quantification of US contrast agent flow into the tumor can reflect changes in tumor blood flow during and after interventional procedures such as radiofrequency ablation, chemoembolization or antiangiogenic therapies [16]. In these cases, in addition to anatomic assessments, dynamic IV CEUS also provides analysis of contrast kinetics within lesions by calculation of time-intensity curves [16]. These calculations include peak enhancement (PE), time to PE, rate of enhancement, and areas under the curve (AUC) such as the total AUC and AUC during wash-in and wash-out phases [16]. This information provides objective, quantitative, and comparable information and can act as surrogate markers of tumor vascularity to predict tumor response or progression earlier in comparison with other conventional modalities.

Blunt abdominal trauma

Trauma is one of the leading causes of morbidity and mortality in childhood. The abdomen is the third most commonly injured anatomic region in children, following head and extremities. Anatomical differences in children make them more vulnerable to major solid organ injuries with minor applied forces [42].

The hemodynamic status of the patient primarily dictates initial management after abdominal trauma and diagnostic imaging plays a major role in the overall decision-making process. For hemodynamically unstable children, the greatest challenge is prioritizing injuries, and imaging of these patients must be kept to a minimum to avoid delays in any therapeutic intervention. Hemodynamically stable children will commonly undergo radiologic investigations. Focused abdominal sonography in trauma US (FAST-US) is usually the initial imaging approach to assess for the presence of free intraperitoneal fluid and identify solid parenchymal injuries. However, it has been demonstrated that not all pediatric patients with traumatic injury have free intraperitoneal fluid and more important, children with normal findings on FAST-US examination may in fact have missed injuries [43, 44].

Contrast-enhanced computed tomography (CT) is undoubtedly the gold standard in evaluating and triaging abdominal injuries. In cases of serious polytrauma or multiple injured patients, there are significant direct benefits associated with the use of CT mainly related to the rapid access and performance of the examination combined with the panoramic field of view, and high

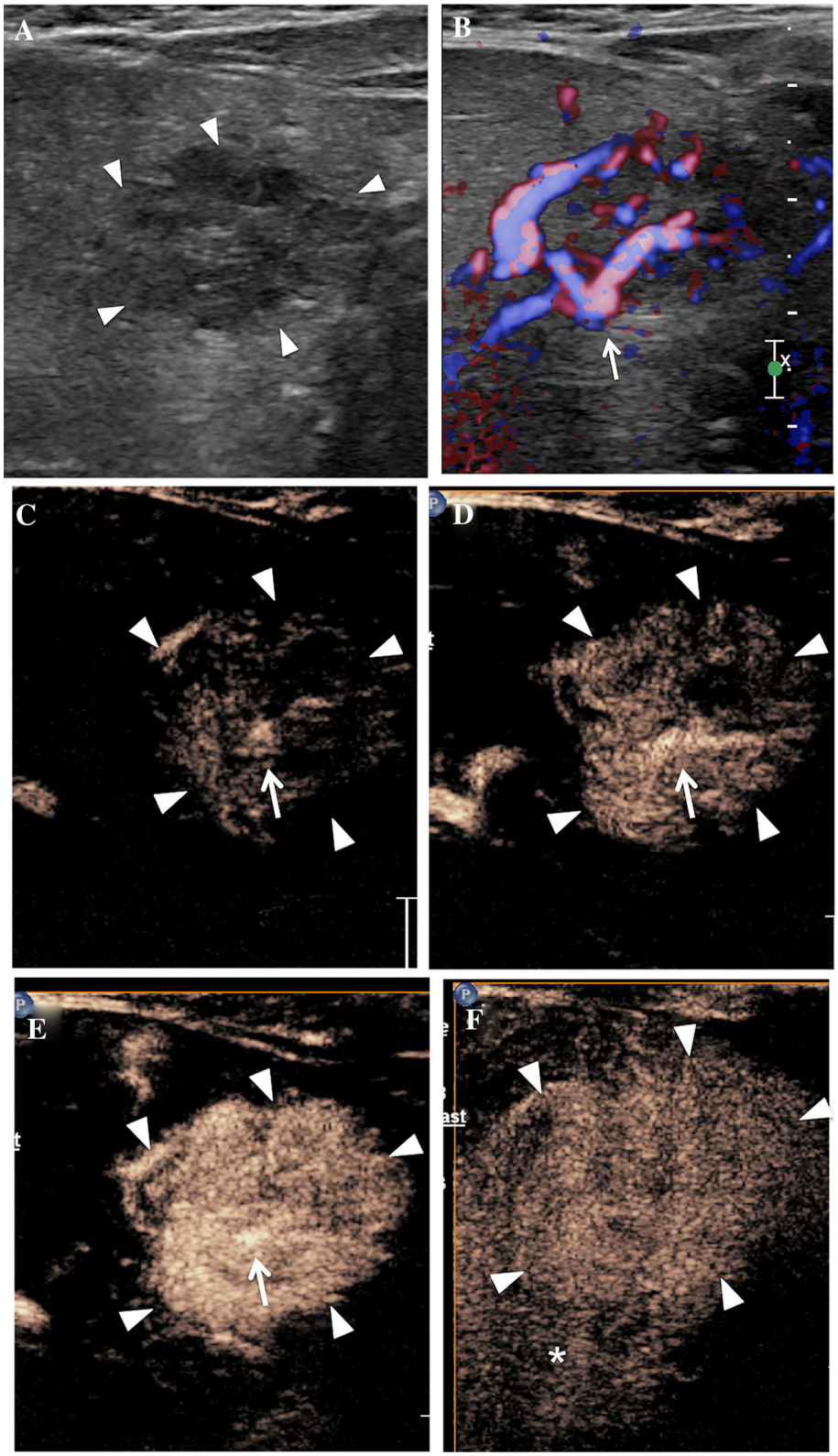

Fig. 1. IV CEUS. Focal nodular hyperplasia. 9-month-old boy with Wolff-Hirschhorn syndrome. Incidentally detected focal liver lesion. **A** Baseline gray scale ultrasound. A predominantly hypoechoic and slightly heterogeneous liver lesion (arrowheads) is seen in the left hepatic lobe. **B** On color Doppler examination, the lesion demonstrates spoke-wheel pattern of vessels centrally (arrow). **C--F** Contrast-enhanced Ultrasound. The lesion (arrowheads) demonstrates early arterial enhancement with the presence of large feeding arterial branches centrally (arrow). In the portal-venous phase, the lesion becomes iso-enhancing compared with the adjacent liver parenchyma (asterisk). No unenhanced central scar is detected. These findings are consistent with focal nodular hyperplasia. No other investigation performed.

diagnostic accuracy that helps to decide operative versus non-operative management [45].

However, in the recent decades, IV CEUS is gaining an important role in the imaging algorithm of selected cases of children with low-energy impact trauma and isolated solid abdominal organ injuries, where a CT may not be fully or at least initially justified [46, 47]. Among the advantages of IV CEUS in this setting is that it can

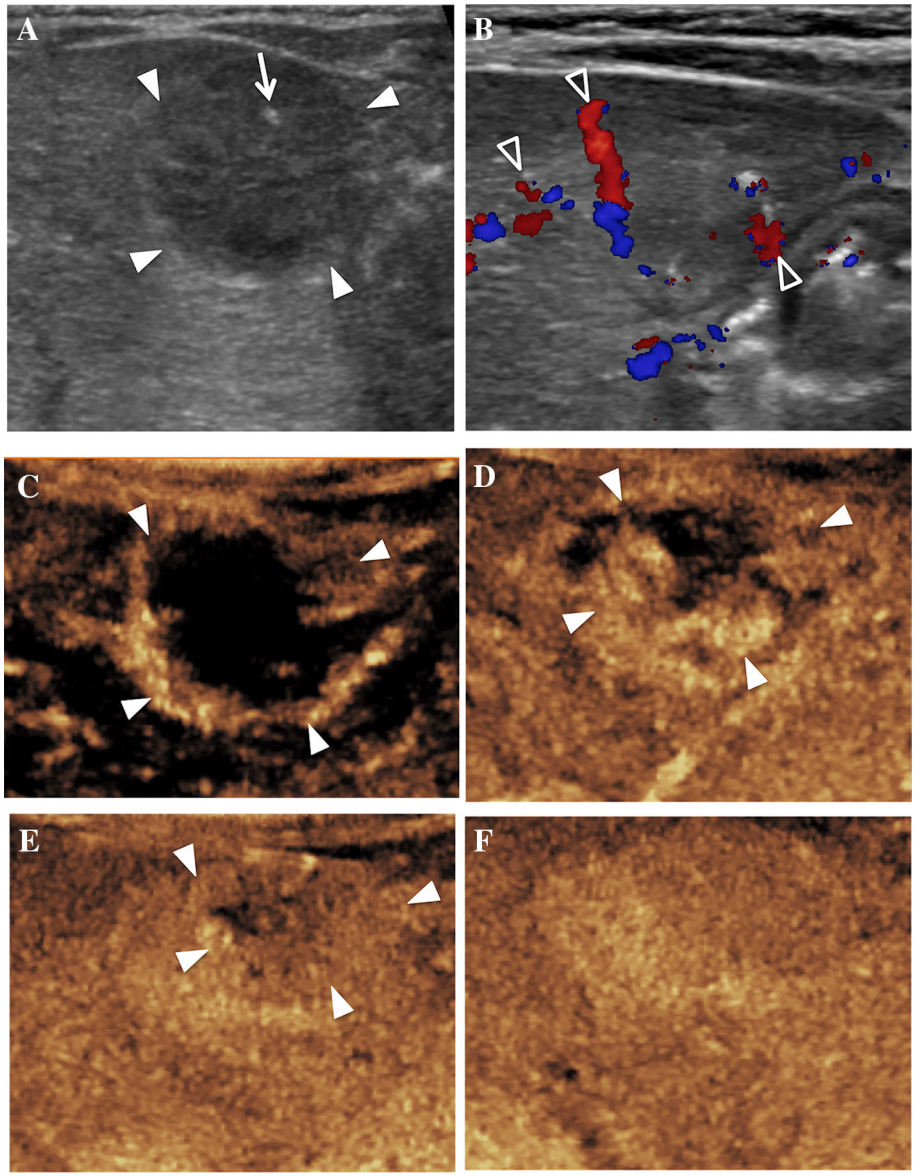

Fig. 2. IV CEUS. Solitary infantile hepatic hemangioma. 2-month-old boy presents with vomiting and abdominal pain. Ultrasound was requested to rule out pyloric stenosis. **A** Baseline gray scale ultrasound. Incidental note is made of a 2 cm in maximum diameter, spherical, predominantly hypoechoic, solid lesion (solid arrowheads) in the anterior left hepatic lobe with presence of an internal hyperechoic focus consistent with calcification (arrow). **B** Color Doppler shows several vessels around the periphery of the lesion (open arrowheads) with a few vessels extending into the lesion. **C--F** Contrast-enhanced Ultrasound. Following intravenous injection of the ultrasound contrast agent, there is early peripheral nodular enhancement of the lesion (arrowheads) with progressive centripetal filling and complete-homogenous enhancement in the delayed phase. These findings are consistent with infantile hepatic hemangioma. No other investigation performed.

be performed quickly and portably at the bedside without interfering with resuscitation. Images can be interpreted in real-time and communicated quickly to the clinical team [15].

Traumatic solid organ injuries appear on IV CEUS as hypoechoic, nonenhancing defects with clear and irregular margins compared to the adjacent normally perfused parenchyma that enhances homogenously [48]. IV CEUS can accurately grade the lesions based on their location and extent with respect to the organ capsule (Fig. 4) [49]. Intravenous CEUS is also sensitive in the detection of active bleeding from parenchymal injuries. Active bleeding will manifest as an area of contrast pooling that continuously changes in size and shape during the different IV CEUS vascular phases, either locally within the lesion or accumulating outside of the organ capsule (Fig. 5) [50]. In addition, enhancement of the parenchymal organs allows for the more conspicuous identification of abnormal intraperitoneal fluid collections representing hematomas. Hematomas appear as nonenhancing anechoic fluid collections accumulated in the peritoneal spaces.

However, IV CEUS is not suitable in cases of multisystem trauma, if neurologic, thoracic, mesenteric or retroperitoneal injuries are suspected. In addition, one should be aware that renal collecting system injuries are not visualized with IV CEUS because the US contrast agents are not excreted into the pelvicalyceal system and ureters [51].

The decision to use IV CEUS in the evaluation of trauma should always be a matter of clinical judgment, tailored to the individual circumstances of the patient and following consultation between the radiologist and requesting physician. Currently, we do not suggest that IV CEUS replace CT, but should be considered as a first-

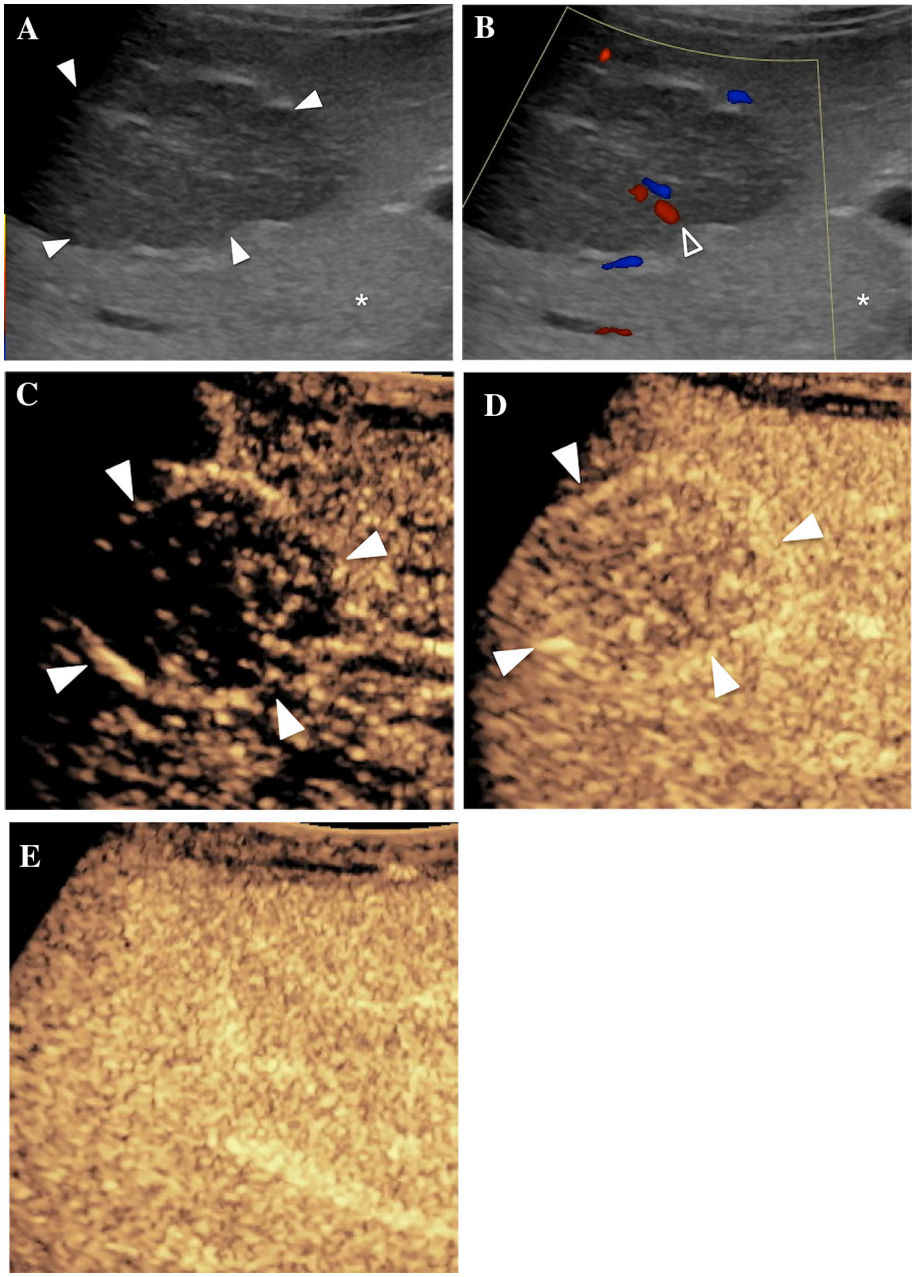

Fig. 3. IV CEUS. Focal Fatty Sparring. 1.5-year-old boy referred for ultrasound evaluation of clinically suspected hepatosplenomegaly, hepatitis, and cholestasis. **A** Baseline gray scale ultrasound. A geographic, relative hypoechoic area (solid arrowheads) is noted in the right hepatic lobe. **B** On Color Doppler imaging, normal vessels are seen coursing through this area (open arrowhead). The remaining liver is relatively hyperechoic suggestive of fatty liver (asterisk). **C--E** Contrast-enhanced Ultrasound. Following intravenous injection of the ultrasound contrast agent, there is slight delay in opacification of the large geographic hypoechoic lesion. The remaining vascular phases show similar enhancement characteristics as the adjacent liver. Overall, these are benign enhancement features. This region represents an area of focal fatty sparing in an otherwise fatty liver. No other investigation performed.

line alternative in select hemodynamically stable children who have sustained low-energy blunt abdominal trauma. However, its greater role may be in the follow-up of known injuries that are treated conservatively. In these situations, serial IV CEUS examinations can monitor the evolution of solid organ traumatic injuries, thus curtailing the need for repeated contrast-enhanced CT imaging.

Intracavitary CEUS applications: dose and procedural considerations

The most longstanding and well-established intracavitary pediatric CEUS application is contrast-enhanced voiding urosonography (ceVUS). This is a pediatric-specific application performed with the intravesical administration of the US contrast agent for the detection and grading of vesicoureteral reflux in children [52, 53].

The basic procedural steps for ceVUS performance are the following: First, the US contrast agent is reconstituted according to the manufacturer's instructions. Then, the bladder is catheterized under aseptic conditions and completely emptied. A bag of normal saline is connected through a three-way valve with the bladder catheter and is hung approximately 60 cm above the bladder level in order to facilitate retrograde urinary bladder filling via gravity. The volume of the normal saline bag corresponds at least to the expected for age bladder capacity that is calculated according to the Koff formula: Expected bladder capacity (mL) = (age in

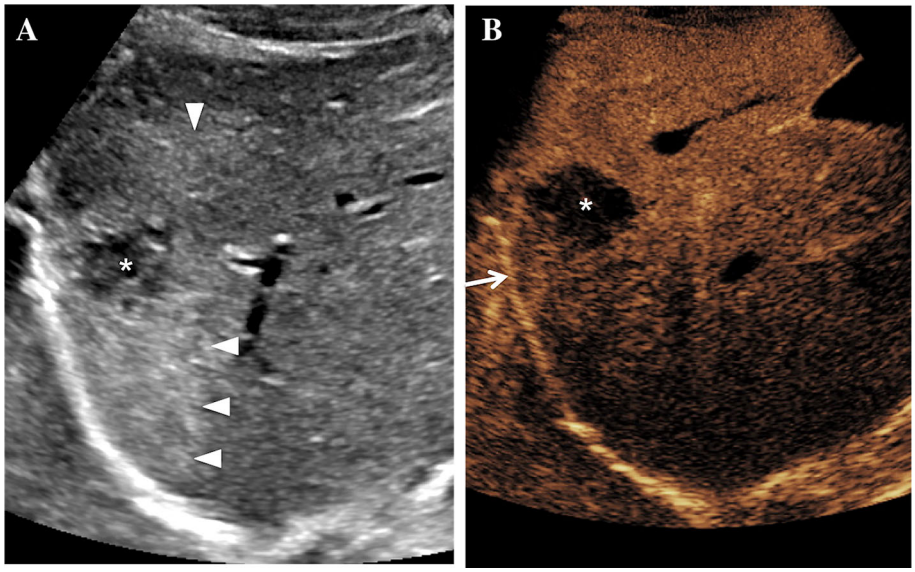

Fig. 4. IV CEUS. Blunt abdominal trauma. 15-year-old boy sustained handlebar injury to the abdomen, presented with abdominal pain and mildly elevated liver enzymes. **A** Initial gray scale ultrasound of the abdomen revealed a heterogeneous subcapsular lesion in the subdiaphragmatic region of the right liver lobe (asterisk), surrounded by diffusely increased echogenicity (arrowheads). **B** Contrast-enhanced Ultrasound. Following intravenous injection of the ultrasound contrast agent, the lesion becomes very well demarcated due to lack of enhancement. The exact size of the lesion can be clearly recognized and measured. The lesion does not reach the liver capsule (arrow), and no subcapsular hematoma is visualized. No other nonenhancing areas of the liver were noted. These findings are consistent with liver contusion/hematoma Grade II liver injury based on the American Association for the Surgery of Trauma (ASST) guidelines. The surrounding liver parenchyma enhances homogenously; therefore, the initial slightly increased peripheral enhancement is considered to correspond to edema.

years + 2) × 30 [54]. Two techniques have been described for the intravesical administration of the reconstituted US contrast agent [55, 56]. The first technique requires the partial filling of the bladder with normal saline via gravity drip followed by direct intravesical injection of the US contrast agent through the three-way valve of the catheter. After contrast injection into the bladder, the bladder is continuously filled with normal saline via gravity infusion [57]. The second technique involves the dilution of the US contrast medium into the normal saline bag and the subsequent filling of the urinary bladder with the US contrast agent/normal saline solution via gravity infusion [56]. Irrespective of the technique used, the use of the diluted US contrast medium reduces the risk of any potential subclinical biologic effects induced from the interaction between the bladder uroepithelium and the concentrated form of the US contrast agent [55].

Recommended pediatric intravesical dosing based on the current literature

A dose of 0.5–1 mL SonoVue® is reported for ceVUS with direct injection of the contrast agent into the bladder [13]. Using an infusion technique, a 0.2% solution of the contrast agent Optison™ and normal saline is sufficient [19, 20, 58]. Our experience with the infusion dose of a Lumason® solution with normal saline has been similar to that of Optison™. As with intravenous dosing, intravesical contrast dose may vary with the use of different US equipment and should be optimized for image quality.

Following US contrast agent administration, real-time sonographic evaluation of the urinary tract is performed by scanning the urinary bladder including the retrovesical space to evaluate the distal ureters, and both kidneys alternatively in prone and/or supine positions, during bladder filling, voiding and after voiding.

The presence of echogenic microbubbles within the ureter, the renal pelvis and/or calyces represents retrograde urine flow in keeping with vesicoureteral reflux, which can be classified into 5 grades (similar to the current grading system used for conventional VCUGs), based on the involved parts of the urinary tract and the degree of the resultant pelvicalyceal or ureteral dilation and tortuosity (Fig. 6) [59].

Cyclic ceVUS with multiple consecutive filling and voiding cycles of the bladder is usually performed in neonates and infants who tend to void at volumes lower than their bladder capacity. A cyclic examination increases the reflux detection rate [60].

At the end of the examination, transperineal or transabdominal scanning of the urethra is performed in a dedicated ceVUS cycle for the delineation of urethral anatomy and identification of any associated pathology

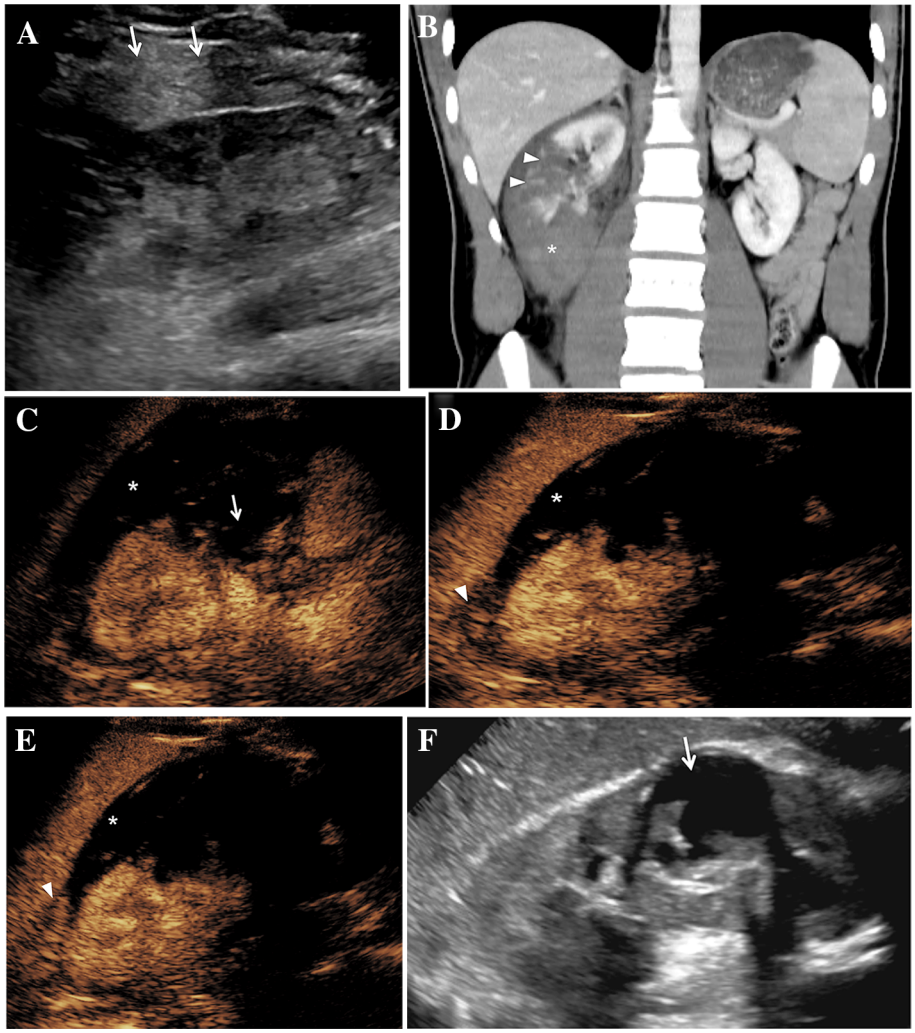

Fig. 5. IV CEUS. Active Bleeding. 16-year-old boy kneed in the abdomen during a baseball game. **A** Initial gray-scale ultrasound images show an acute perinephric hematoma - around the right kidney (arrows). **B** Contrast-enhanced Computed Tomography (CT), coronal reformat. A shattered right kidney (arrowheads) with a large perinephric hematoma (asterisk). **C** There was concern for active bleeding due to a sudden drop in hemoglobin from 11 to 8 mmol/L. Contrast-enhanced ultrasound was performed. Following intravenous injection of the ultrasound contrast agent, there is large wedge-shaped hypoechoic area (arrow) through the interpolar region of the right kidney, corresponding to the renal fracture and correlating with the recent CT. A surrounding anechoic perinephric hematoma (asterisk) is again identified. **D--E** There is an area of contrast pooling (arrowhead) accumulating within the hematoma (asterisk) around the upper pole of the kidney with change in volume during real-time scanning, indicative of active bleeding. **F** Follow-up gray-scale ultrasound shows the laceration of the right mid-pole of the kidney (arrow) significantly smaller in size.

including posterior urethral valves, strictures or diverticula [61].

Several comparative studies between ceVUS and the conventional ionizing methods for reflux detection, namely VCUG and radionuclide cystography (RNC) have demonstrated that ceVUS is not only more sensitive to detect reflux in children but also more accurate in grading its severity [53]. In total, nine comparative studies, including in total 684 children who underwent consecutive performance of ceVUS and VCUG during the same session, demonstrated the high diagnostic accuracy of ceVUS in VUR detection rate with sensitivity and specificity of 94% and 95%, respectively [62–70]. In addition, one previous study showed that 56% of reflux cases were missed by VCUG and were only detected by ceVUS [70, 71]. These cases were of higher grade and thus of greater clinical significance. Among the reasons to explain this discordance is that ceVUS is very sensitive to detect tiny amounts of refluxing microbubbles compared with VCUG that needs a larger volume of refluxing contrast agent. In addition, the absence of ionizing radiation permits continuous, real-time scanning of the urinary tract and thus better evaluation of the dynamic nature of the intermittent reflux phe-

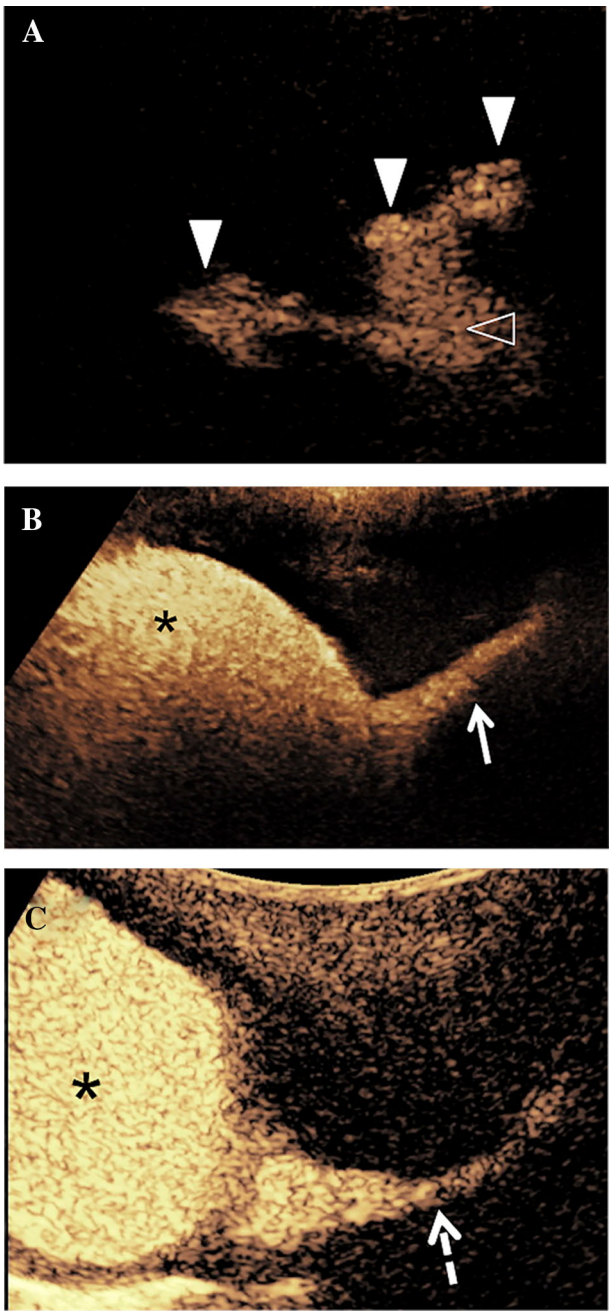

Fig. 6. Contrast-enhanced voiding urosonography. **A**, **B** 6.3-year-old girl referred for follow-up of previously known vesicoureteral reflux. Echogenic microbubbles are seen in the pelvis (open arrowhead) and calyces (solid arrowheads) of the right kidney which are mildly dilated in keeping with Grade 2 reflux. **B** Urinary bladder (asterisk) is filled with echogenic microbubbles. The proximal segment of the female urethra (arrow) is delineated during the beginning of the voiding phase and has normal morphology. **C** Different male patient. Urinary bladder (asterisk) is filled with echogenic microbubbles. The male urethra (dashed arrow) is delineated throughout its course during voiding phase with no evidence of intraluminal pathology.

nomenon. More important, in six studies, including in total 1660 children, ceVUS was the first and only imaging study for VUR detection that was performed, replacing completely the ionizing VCUG and RNC [55, 56, 72–75].

Contrast-enhanced voiding urosonography: safety considerations

There is a large volume of safety data regarding the intravesical administration of US contrast agents. To date, 15 original studies were published on ceVUS with intravesical administration of SonoVue® [55, 56, 62–70, 72–75] and 2 original studies were published on ceVUS with intravesical administration of Optison™ [19, 20], including in total more than 2300 children. In the majority of these studies, clinical evaluation for possible adverse events was performed, and safety data were collected and reported.

No serious events were described with the intravesical administration of these US contrast agents [4, 55]. However, in the largest study dedicated to safety, including 1010 children who underwent only ceVUS examination, a few minor adverse events following the procedure occurred in 37 children, accounting for 3.66% of the study population. These symptoms include dysuria, urinary retention, abdominal pain, anxiety and crying during micturition, blood and mucous discharge, increased frequency of micturition, vomiting, perineal irritation, and urinary tract infection [55]. The type and the frequency of these adverse events, were similar to those encountered with VCUG or RNC and were most likely related to the inevitable bladder catheterization rather than the contrast agent itself [76].

So far, only clinically based evaluations of adverse events related to the intravesical administration of US contrast agents have been conducted, but no in vitro study has ever evaluated potential subclinical bio effects [77]. However, the intravesical administration of US contrast agents appears to have a much higher safety margin compared to the intravenous use of the same US contrast agents due to the following reasons: (a) within the bladder, the administered ultrasound contrast agent is highly diluted, and thus the microbubble concentration is low, occupying a relatively large volume and not confined in a small space such as in a capillary; (b) in the renal pelvis and calyces, the US contrast agent is in a relatively large space and mixed with normal saline and urine; and (c) once reflux is documented, there is no need to continue scanning, and thus, the actual scan time of the renal pelvis filled with microbubbles does not exceed a few seconds.

Conclusions

Over the recent decades, the diagnostic spectrum and applicability of pediatric CEUS have increased world-

wide. The recent FDA approval of the most commonly used SonoVue®/Lumason® US contrast agent for pediatric liver and intravesical applications gives new drive to pediatric CEUS worldwide. In the appropriate clinical context, pediatric CEUS can provide safe and immediate diagnosis, avoiding unnecessary radiation exposure and the need for sedation in children while reducing further referrals and examination costs.

Compliance with ethical standards

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Conflict of interest All authors have no conflict of interest to declare.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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