Contrast-enhanced ultrasound (CEUS) in children: Ready for prime time in the United States!

For the SPR newsletter and/or SPR CEUS website: based on the presentation given at the IPR 2011 in London by Kassa Darge, MD, PhD, The Children’s Hospital of Philadelphia (CHOP) entitled:
“Present state of contrast-enhanced ultrasound beyond Europe – in the USA”

Introduction

Ultrasound contrast agents (USCAs) have been in clinical use for more than 25 years, and like many imaging advances, are primarily used in adults. USCAs are microscopic microbubbles filled with different types of gases. On the US screen they appear as echogenic dots. They can be administered intravenously and, being blood pool agents, remain intravascular, thus enhancing the visibility of the vascular structures. In addition to making larger vessels visible, they can demonstrate microperfusion, thus revealing tissue ischemia. In combination with Doppler examination, they enhance the signal of color, power, and spectral Doppler. The longstanding and most widespread IV use of USCAs is in echocardiography. Intracavitary use of USCAs includes the intravesical administration for diagnosis of vesicoureteric reflux (VUR) or the intrauterine injection for sonographic hysterosalpingography. The elimination of radiation exposure and the possible cost savings by reducing the number of potential additional CT or MR examinations are important advantages of CEUS. The clinical safety profile of USCAs is excellent, with no nephrotoxicity.

There have been significant developments in US technology resulting in advanced contrast-specific imaging modalities. The latest ones incorporate primarily low mechanical index (low MI) imaging allowing for dynamic scan of the microbubbles without destroying them. There is the possibility of short-term destruction of the microbubbles making perfusion assessment possible. The visualization of the microbubbles is greatly enhanced with color overlay and background subtraction options.

CEUS in children - Europe

It was in the late 90s in Europe that non-cardiac pediatric use of USCAs really started to gain impetus. At present contrast-enhanced voiding urosonography (ceVUS) for VUR diagnosis is the main application of USCAs in children. This uniquely pediatric use of USCA has gained widespread acceptance over the past few years. The most recent meta-analysis of all the comparative studies of ceVUS with voiding cystourethrography (VCUG) and direct radionuclide cystography (DRNC) in children included more than 2300 children with over 4600 pelvi-ureteric units. Using VCUG as the reference method, ceVUS had a sensitivity of 90% and specificity of 92%. There is also a high correlation of the reflux grading of the two methods. It is important to note that more and higher grade VUR, up to 10%, are detected on ceVUS than on VCUG. The combination of contrast-enhanced urethrosonography with ceVUS has enabled exquisite depiction of urethral pathologies, including posterior urethral valves. The visualization of intrarenal reflux is easier with ceVUS. VCUG and DRNC are increasingly being replaced with ceVUS.

The IV use of USCAs in children has not kept stride with ceVUS. Even centers with many publications on ceVUS have not contributed major studies towards pediatric IV CEUS. There are two important issues that may be cited as possible factors for this lack of development. The most common non-cardiac indications in adults are for evaluation of focal hepatic lesions and tumors. These of course are not as common in children, thus limiting the experience of IV CEUS. Furthermore, the rarity of such findings and the need for definite diagnosis triggers in most pediatric cases further evaluation with CT and/or MRI. The IV CEUS performed occasionally in such cases are seen as just complimentary, without preventing the additional studies. Not being able to replace to a significant extent another imaging study slows down the widespread use of a new modality. The indications of IV CEUS in children reported to date include focal liver lesion characterization, abdominal solid tumor treatment follow-up, blunt abdominal trauma, pyelonephritis, assessment of vascular supply in organ transplants, inflammatory bowel disease, testicular/ovarian torsion, femoral head perfusion and arthritis assessment. In animals, brain perfusion has been studied. Targeted drug delivery using USCAs is an important application that has not yet been used in children.

CEUS in the United States

Currently, in the United States there are only 2 USCAs approved by the Food and Drug Administration (FDA), both for IV use for echocardiography in adults. These second generation USCAs contain the gas perfluorocarbon (Definity®, Lanthaeus Medical Imaging, N. Billerica, MA and Optison®, General Electric, Princeton, NJ). There are no approved USCAs available for non-cardiac use. This has not deterred the relatively large scale off-label non-cardiac use of USCAs in adults. There is an
ongoing multi-center phase III study on “SonoVue®-enhanced US versus unenhanced US for focal liver lesion characterization” sponsored by the manufacturer of the USCA (Bracco, Milan, Italy). The study is anticipated to be completed at the end of 2011.

Why is non-cardiac CEUS much more advanced and widely available in Europe than in the USA? To answer this question one has to consider differences in both practice pattern and regulatory aspects. In the USA the relative importance of US among imaging studies is not as high; US is primarily done by sonographers and not radiologists; US use by non-radiology specialties is still in its early stages and the reimbursement for CEUS will not be as high as for CT or MRI. A more lengthy and costly regulatory pathway is restraining factor for the USCA manufacturers. When it comes to pediatric applications the less attractive profit margins are additional drawbacks. The lobby for US and particularly for CEUS is relatively less powerful. Fortunately, with regard to the latter there are increasingly positive changes with more intensive activities by the American Institute of Ultrasound in Medicine (AIUM) and the establishment of the International Contrast Ultrasound Society (ICUS). Additional impetus for promoting the use of USCAs comes from the increasing awareness of radiation risk, particularly in children, advanced by the “Image Gently” campaign. The fact that MRI with contrast is not a completely safe study due to the possibility of nephrogenic systemic fibrosis also promotes the search for safer alternatives. Recent publications suggesting that repeated anesthesia under 2 years of age may carry a small risk of developmental delay, add another concern in pediatric MRI.

Pediatric CEUS in the United States

What is the current status of pediatric CEUS in the USA? Important in-vitro and animal studies using USCAs with pediatric indications in mind have been carried out in the States. One of the first publications on ceVUS in children came from an American urologist using custom-made USCA. It is also encouraging to realize that currently, at least in one pediatric oncologic center, an IV CEUS clinical study with off-label use is taking place. There is increasing demand by pediatric oncologists to use USCA, particularly for treatment monitoring. The SPR board has taken a decisive step in officially endorsing the use of CEUS in children and by establishing a CEUS taskforce. This taskforce has been assigned with the mission of raising the awareness about CEUS in the pediatric radiology community and also facilitating the approval of USCA for pediatric indications through the FDA, in collaboration with the USCA manufacturers. An active role by the users (pediatric radiologists) is of utmost importance in order to have USCAs approved for pediatric use. The chance that USCA manufacturers will unilaterally pursue clinical trials leading to approval of pediatric indications is remote. The best hope is for collaboration between industry and the SPR. The uroradiology committee of the European Society of Pediatric Radiology (ESPR) is undertaking a similar concerted effort, and thus a close rapport with the SPR CEUS taskforce is planned.

An official FDA approval will entail multicenter studies. Where should the focus be of the initial studies? There are three main advantages to try to work on approval of USCAs for ceVUS: (1) there is a large published data base, (2) ceVUS can completely replace conventional imaging and (3) VUR is a common problem. When it comes to IV use, the question arises as to which indication to work on first. Here again, a study that has the potential to replace another one completely, or one which can provide answers to questions not possible to get from other imaging modalities, has the better chance of future widespread application. Another factor to consider is the incidence of the pathology selected for evaluation. The feasibility of the practical part of conducting such an IV CEUS study needs to be taken into consideration. Characterization and particularly post-treatment follow-up of solid tumors of the abdomen may be a good start. For this we already have interested partners in the pediatric oncology community. Furthermore, the future of microbubbles-facilitated drug delivery is in oncology. A second indication for possible initial multicenter study is evaluation of femoral head perfusion after hip reduction. Currently, primarily MRI is carried out and a replacement with CEUS would have significant practical impact. Evaluation of transplant perfusion, particularly enhancing the depiction of the vascular supply, with CEUS has the potential not only of making a bedside US examination easier, but may curtail the need for more complex angiographic studies.

In conclusion, with the continued support of the SPR and the concerted effort of the CEUS taskforce, pediatric CEUS may soon be ready for prime time in the USA.

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