

Contrast-Enhanced US: Effective, Safe, Underutilized

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Microbubbles as an ultrasound-enhancing agent (UEA) improve the quality of acquired images for a range of clinical indications in both cardiology and radiology, offering real-time, well-tolerated visualization of vital structures. Despite proven benefits of contrast-enhanced US (CEUS)—including lack of nephrotoxicity or ionizing radiation—concerns about UEA safety have seemingly hindered its widespread adoption in the United States, after a 2007 FDA black box warning noted the potential for rare but serious cardiopulmonary reactions. Numerous studies went on to show that the most serious adverse events (SAEs) happened in patients with severe, underlying cardiac or pulmonary illnesses, the true risk of these agents was extremely low, and UEAs were well tolerated even in critically ill patients.¹⁻³ Despite recent anecdotal reports of CEUS's steady clinical growth—and documented steady market size growth⁴—reticence remains about its use.

Seeking to allay fears and highlight the safety profile of CEUS, Jordan B. Strom, MD, MSc, Director of the Echocardiography Laboratory in the Division of Cardiovascular Medicine at Beth Israel Deaconess Medical Center in Boston, and fellow researchers performed a large, nationwide, claims-based analysis of echocardiograms administered with and without UEAs, from 2018 to 2022. Results published last May in the *Journal of the American Heart Association*⁵ found that SAEs associated with UEAs are “uncommon,” occurring in 1 in 10,000 cases.

“My goal was to test the continued safety of these agents, ultimately finding that the risks [of CEUS]

continue to be vastly exceeded by the benefits,” Dr Strom says.

Similar studies have demonstrated the safety of CEUS in radiology, which has grown in use in recent years, according to Richard G. Barr, MD, PhD, Professor of Radiology at Northeastern Ohio Medical University, radiologist at Southwoods Health, and Editor-in-Chief of the *Journal of Ultrasound in Medicine*.

“Our safety data⁶⁻⁸ is very similar to what [Dr Strom] found,” reports Dr Barr, noting zero deaths in a review of 609,582 patient exams across 118 publications; only 22 SAEs at a rate of less than 1 in 25,000, with adverse events (AEs) occurring at similar rates to contrast-enhanced CT and MRI exams.

David T. Fetzer, MD, Associate Professor of Abdominal Imaging and Director of Ultrasound in the Department of Radiology at UT Southwestern Medical Center, a self-described “busy non-cardiac user of CEUS,” addresses the startling overstatement of rare AEs linked to their use.

“Ultrasound, and particularly microbubble contrast agents, have been held to a different bar than what we have seen with iodinated agents in CT and gadolinium agents in MRI. We all know that there are rare, but true, adverse events in CT and MRI, and there isn't the same overreaction, compared to the reaction we see when there are events in ultrasound,” Dr Fetzer says. “Why is there such a stigma against an otherwise incredibly safe contrast agent? I don't know how many papers we have to come out with as a community to show its relative safety compared to widely used medica-

tions and agents to continue to validate contrast-enhanced ultrasound's utility."

Dr Strom agrees that while medicine inherently involves a level of risk—for example, in the cath lab—the expectation of any treatment is for the benefit to exceed the risk.

"In terms of imaging [in the echo lab], we have to think about [UEAs] in the same way. We have a lot of benefits, and we have a very, very low risk. It makes sense for us to use these agents, and they're not being used," he explains. "We know 10% to 20% of people potentially have an indication for [ultrasound] contrast. We only use contrast in the U.S. in about 6.8% of cardiac ultrasounds."

Cardiac Usage and Data

Dr Strom's recent study, based on data from more than 11.4 million patients, found that SAEs associated with UEAs were "uncommon"—1 in 10,000 cases—and that this low risk was consistent with results of previous studies and was similar across the 4 years and commercially available agents (Lumason from Bracco Diagnostics; Definity from Lantheus Medical Imaging; and Optison from GE Healthcare).

Further, the study evaluated rates of death, anaphylaxis, myocardial infarction, ventricular tachycardia, or cardiac arrest within 2 days of transthoracic echocardiography/stress echocardiography among adults both receiving and not receiving UEAs, and the odds of death were actually lower in patients who received them when accounting for differences in those who receive and don't receive UEAs.

"These findings overall signify the continued safety of UEAs in contemporary clinical practice," according to Dr Strom, who uses UEAs in about 40% of echo lab cases, up from 2.6% from 2000 to 2018.¹⁰ CEUS enhances visualization of left ventricular pacification in the setting of poor endocardial border resolution, assessment of wall motion abnormalities, and identification of masses, aneurysms, apical abnormalities of the heart, and cardiomyopathies, among other cardiac and vascular conditions,¹¹ he says.

"We've really grown the program to allow for sonographers and other technical staff to be able to give UEAs independently within their scope of practice," Dr Strom says of his organization's culture of safety, noting that CEUS may be underutilized nationwide due to sonographer's lack of training with intravenous medication administration, which creates workflow hurdles.

When administering UEAs, it is critical that staff be properly trained in recognition and management of allergic reactions, including the use of an allergy kit, he adds.

"Anaphylaxis is a big issue for a very small number of people, but we need to identify [them] ahead of time," continues Dr Strom, who

is currently working with an allergy group from the Vanderbilt University Medical Center in Nashville to create an echo lab screening tool for polyethylene glycol (PEG) allergy.

In acute intensive care patients, suboptimal image quality of standard echocardiography can lead to downstream or duplicative tests, Dr Strom notes. When making a critical decision, real-time CEUS enhances diagnostic confidence efficiently.

"I strongly feel that we should use all the tools at our disposal to get the best possible diagnostic imaging upfront, so we're making the right decisions at the right time and avoiding repeat testing for our patients," Dr Strom says. "My hope is that the safety data will be reassuring."

Radiology Applications

While used at significantly lower volumes than in cardiology, CEUS is an effective technique for improving the visualization, characterization, and diagnostic accuracy of lesions and vascular structures, and most commonly used in kidney and liver imaging and exams in pediatric and pregnant patients. The tool can be used to assess lesions at the point of care—for example, in the emergency room—and facilitate their characterization to expedite next steps, says Dr Barr, who says renal masses are better diagnosed using thinner-slice CEUS than CT and MR.

"We're getting to the point now where we can almost make a histological diagnosis by evaluating the enhancement pattern...because we have this high frame rate and really good enhancement," explains Dr Barr.

In patients with chronic liver disease being screened for the development of hepatocellular carcinoma (HCC), giving contrast upon lesion detection can facilitate a diagnosis, he adds. "Several studies have shown that 85% of the time ... they don't need to go on for further CT or MR," which saves time and worry for the patient.

While radiology sonographers are trained in managing AEs relating to contrast use, from a safety standpoint, Dr Barr reiterates that SAEs are rare.

"I'm estimating between about 7,000 and 8,000 cases, we've only had one reaction [for which] we actually had to monitor the patient and give medication, and no deaths. We see more reactions with CT and MR than we see with contrast ultrasound," Dr Barr says, adding that ahead of agent administration, it is important to inquire about a known PEG allergy.

Dr Fetzer, who uses CEUS for renal and liver mass characterization and US-guided intervention, appreciates the benefits of same-day CEUS for incidental or surveillance findings.

"[If] we see a mass [on a standard grayscale image], we then do contrast-enhanced ultrasound and are able to diagnose HCC that same day, which accelerates workup," Dr Fetzer says, noting an improved patient experience given long wait times for MRIs.

“We can, with a clear conscious, recommend contrast-enhanced ultrasound because we know for a fact that it has no nephrotoxicity. We can often get the same or similar diagnostic information ... without the worry that comes along with CT and MRI agents,” Dr Fetzter adds, noting the tool is useful for pregnant women since the agents do not cross the placenta into fetal circulation.

Dr Fetzter, who is co-chair of the LI-RADS working group for CEUS, contributed to research and creation of the algorithm for diagnosing HCC and for evaluating HCC after non-radiation-based liver-directed treatment, demonstrating the value of CEUS and enabling higher volumes of real-world data. CEUS can now be used for HCC diagnosis and for exception points in the management of patients waiting for liver transplantation.

Continuing to reiterate the relative safety of CEUS should reduce hesitancy of use throughout the imaging community, particularly among trained sonographers, concludes Dr Fetzter.

“There’s the misconception that a radiologist always has to be involved [for CEUS]. Yes, you still need two pairs of hands, but that second pair of hands does not need to be a radiologist. You build a team of people who are comfortable administering ultrasound contrast. Highlighting contrast ultrasound safety may help with that adoption and lower the barrier for sonographers to learn it and do it well.”

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