AIUM Practice Parameter for the Performance of Contrast-Enhanced Ultrasound Examinations

Introduction

The American Institute of Ultrasound in Medicine (AIUM) is a multidisciplinary association dedicated to advancing the safe and effective use of ultrasound (US) in medicine through professional and public education, research, development of clinical practice parameters, and accreditation of practices performing US examinations.

The *AIUM Practice Parameter for the Performance of Contrast-Enhanced Ultrasound Examinations* was developed by the AIUM in collaboration with other organizations whose members use US for performing this examination(s) (see "Acknowledgments"). Recommendations for personnel requirements, the request for the examination, documentation, quality assurance, and safety may vary among the organizations and may be addressed by each separately.

This Practice Parameter is intended to provide the medical US community with recommendations for the performance and recording of high-quality US examinations. The parameter reflects what the AIUM considers the appropriate criteria for this type of US examination but is not intended to establish a legal standard of care. Examinations performed in this specialty area are expected to follow the parameter with recognition that deviations may occur depending on the clinical situation.

Indications

Indications for contrast-enhanced ultrasound (CEUS) are based on the current literature recommendations and clinical practice standards.

Contrast-enhanced ultrasound is safe for patients with contraindications to computed tomography (CT) or magnetic resonance imaging (MRI), such as pacemakers, allergies to gadolinium-based or iodinated contrast material, claustrophobia, immobility, or metal implants. Because of its lack of ionizing radiation and ease of performance without sedation, CEUS should be considered as a useful problem-solving tool and as an indicated first-line imaging modality in select settings as indicated below.

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1. Liver
   a. Characterization of focal liver lesions in the noncirrhotic liver.
      i. Further characterize incidentally found liver lesions on US examinations.
      ii. Evaluate incompletely characterized lesions on noncontrast or contrast-enhanced CT or MRI.
   b. Characterization of focal liver lesions in the cirrhotic liver.
      i. Assess nodules detected on surveillance US.
      ii. Assess a Liver Imaging Reporting and Data System (LIRADS) category LR-2, LR-3, LR-4, or LR-M observation on prior contrast-enhanced CT or MRI.
      iii. Detect arterial-phase hyperenhancement when mistiming is suspected as the reason for its absence on prior CT or MRI.
      iv. Assess biopsied lesions with inconclusive histologic results.
   c. Detection of metastases.
   d. Vascular.
      i. Determine hepatic artery, portal vein, and hepatic vein patency.
      ii. Assess transjugular intrahepatic portosystemic shunt patency.
      iii. Distinguish a bland thrombus versus a tumor in a vein.
   e. Response to therapy (ablation or transarterial chemoembolization for hepatic malignancy) for assessment of residual viable disease.[1–3]
   f. Help select appropriate sites for biopsy.
   g. Assess for residual tumor after ablation.
2. Kidney and bladder
   a. Antegrade nephrostogram for evaluation of ureteral patency in the setting of an indwelling nephrostomy tube.[4]
   b. Assessment of native renal perfusion/cortical necrosis in the setting of acute renal failure.
   c. Characterize indeterminate cystic renal lesions.
   d. Differentiate between renal tumors and anatomic variants mimicking renal tumors ("pseudotumors").
   e. Evaluate transplant perfusion: infarct or ischemia.
   f. Identify renal abscesses in complicated acute pyelonephritis.
   g. Follow-up of nonsurgical renal lesions.
   h. Differentiate bladder cancer from hematoma in patients with hematuria.
   i. Improve diagnosis of renal artery stenosis or resolve vascular patency questions.
   j. Pediatric voiding cystourethrography.
      i. Evaluation of prenatally detected hydronephrosis and urinary tract malformations.
      ii. Diagnosis and follow-up vesicoureteral reflux.
      iii. Characterization of urethral abnormalities.
3. Endovascular aortic repair (EVAR) and cerebrovascular assessment
   a. Follow-up of EVAR for the detection and classification of endoleaks.
   b. Differentiate between total carotid and vertebral artery occlusion and residual flow through a tight stenosis.
4. Pancreas
   a. Differentiate between cystic neoplasms and pseudocysts.
   b. Differentiate vascular (solid) from avascular (eg, liquid or necrotic) components of a pancreatic lesion.
   c. Follow-up of indeterminate cystic pancreatic lesions.
   d. Improve the accuracy of percutaneous US-guided pancreatic procedures.
5. Bowel
   a. Estimate disease activity in inflammatory bowel disease.
   b. Monitor the effect of treatment in Crohn disease.
   c. Distinguish abscesses from phlegmons and improve visualization of fistulous tracks.
6. Spleen
   a. Diagnose splenic infarction.
   b. Characterize indeterminate splenic lesions.[5,6]
7. Scrotum
   a. Distinguish vascularized masses from nonvascularized, nontumorous focal testicular lesions.
   b. Identify testicular infarction.
8. Trauma
   a. In stable patients with blunt abdominal trauma, CEUS can be used as an alternative to CT to follow-up solid organ injury, particularly in

children. It can assess for pseudoaneurysms and can be performed at the bedside.

9. Intracavitary injection
   a. Identify needle or confirm catheter position, delineate any cavity or duct, improved tracking of fistulas.
   b. Sonosalpingography.[7]
10. Interventional guidance
   a. Avoid necrotic tissue to improve the cytologic yield in the biopsy of tumors.
   b. Assist in identifying biopsy targets inconspicuous on US imaging or noncontrast CT.
   c. Assess for active bleeding after a procedure.
11. Other
   a. Assessment of vascularized versus nonvascularized lesions can be performed in any other part of the body in addition to the organs listed.
   b. Distinguishing necrotic from nonnecrotic lung in pediatric pneumonia.[8]
   c. Distinguishing complex from simple ovarian cysts.

Qualifications and Responsibilities of Personnel

Physicians (and other providers if applicable) interpreting or performing this type of US examination should meet the specified AIUM Training Guidelines in accordance with AIUM accreditation policies.

Sonographers performing the US examination should be appropriately credentialed in the specialty area in accordance with AIUM accreditation policies.

Request for the Examination

The written or electronic request for a US examination must originate from a physician or other appropriately licensed health care provider or under the provider's direction. The clinical information provided should allow for the performance and interpretation of the appropriate US examination and should be consistent with relevant legal and local health care facility requirements.

Specifications of the Examination

Contrast Dose: In adults, the standard dose for most abdominal applications is 2.4 mL of sulfur hexafluoride lipid microsphere (SHLM) contrast (eg, Lumason; Bracco Diagnostics, Inc, Monroe Township, NJ). In children, the dose is 0.03 mL/kg up to a maximum of 2.4 mL per injection. Intravascular administration of up to 5 mL of SHLM contrast (Lumason) in a single session is approved by the Food and Drug Administration (FDA).

The standard dose of perflutren lipid microsphere (PLM) contrast (eg, Definity; Lantheus Medical Imaging, North Billerica, MA) is 10 μL/kg. The standard dose of perflutren protein microsphere (PPM) contrast (eg, Optison; GE Healthcare, Princeton, NJ) is 0.5 mL. Additional 0.5-mL doses may be given to improve characterization of a finding or overcome artifacts encountered during the initial injection.

Summary of Scanning Protocols

1. Liver

   The hepatic imaging protocol is based on the American College of Radiology (ACR) CEUS Liver Imaging Reporting and Data System recommendations.
   a. A CEUS examination of the liver is usually performed to assess targets clearly identified on precontrast B-mode imaging. Contrast-enhanced ultrasound may be limited in patients with a high body mass index and in patients with severe hepatic steatosis, mainly because of substantial US signal attenuation.
   b. Contrast Dose: The contrast dose specified by the manufacturer should be used for most examinations. Imaging of very superficial liver lesions with higher-frequency transducers will require a contrast dose increase. In addition to patient factors, the contrast dose can be adjusted on the basis of the sensitivity of the equipment used for the CEUS examination.[9,10]
   c. Imaging should be performed continuously from contrast injection until peak arterial-phase enhancement to characterize the presence, intensity, and pattern of arterial-phase enhancement. Alternatively, continuous imaging can be extended beyond peak arterial-phase enhancement until 60 seconds after contrast injection to determine the presence of early washout. After 60 seconds, recording of static images should be performed intermittently (3–5 seconds every 30–60 seconds) to detect late washout and to assess its degree. Continuous

insonation of large portions of the highly vascular liver may result in excessive destruction of microbubbles, thereby limiting assessment for true washout.

d. Imaging of multiple nodules often requires more than 1 contrast injection and careful planning of patient positioning to maximize the use of limited acoustic windows. In patients with multiple liver nodules, 2 or 3 nodules can usually be imaged in a single session.

2. Other abdominal applications[11]
   Most abdominal organs enhance rapidly and intensely 10 to 15 seconds after US contrast administration. The arterial vessels enhance first, followed by diffuse parenchymal enhancement. Contrast enhancement usually persists for 4 to 6 minutes after injection. Unlike CT and MRI contrast agents, microbubbles are not excreted by the kidneys or biliary system. Therefore, no microbubbles are detected in the renal collecting or biliary systems.
   a. Because of the highly vascular nature of the kidney, CEUS examinations can be performed with less than the standard dose.
   b. Imaging should be performed continuously from contrast injection until the imaging target is adequately characterized.

3. Endovascular aneurysm repair (EVAR) and vascular
   a. Contrast Dose: A CEUS examination of the aorta and great vessels is usually performed using a slightly decreased dose of US contrast (ie, 50%–75% of the standard dose [1.5–2.0 mL of SHLM contrast, 0.2 mL of PLM contrast, or 1.0 mL of PPM contrast]).[12]
   b. Imaging
      i. The initial CEUS examination should focus on the time of enhancement of the aneurysmal sac versus the endograft lumen.
         a. Contributing vessels can be identified.
      ii. The examination should continue for at least 10 minutes to ensure that delayed and low-flow endoleaks are identified.

4. Scrotum
   a. Contrast Dose: A CEUS examination of scrotum is performed with high-frequency transducers, requiring higher doses of contrast (4.8 mL of SHLM contrast, 0.4 mL of PLM contrast, or 2 mL of PPM contrast).
   b. Imaging with linear high-frequency transducers should be performed. Contrast-enhanced ultrasound imaging should focus on the arterial phase, as it is the most important aspect of the examination. Imaging should be performed continuously from contrast injection until the imaging target is adequately characterized. The presence and degree of arterial-phase enhancement should be documented.

5. Pediatric voiding urosonography[13,14]
   a. Contrast Dose: To date, published studies have used either SHLM contrast or PPM contrast. The FDA-recommended contrast dose and administration of SHLM contrast are a 1-mL injection into a bladder that is partially filled with normal saline. However, a suspension of US contrast and normal saline can also be infused into the bladder at a dose of approximately 0.2% of the bladder-filling volume. The optimal contrast dose may vary with the use of different US equipment and should be optimized for image quality.
   b. Imaging: Imaging of the bladder, retrovesical space to assess the distal ureters, and both kidneys is performed in the supine, lateral decubitus, and/or prone position during bladder filling. Multiple cycles of bladder filling and voiding are performed in neonates and infants to increase the rate of detection of reflux. The urethra is imaged from either a suprapubic or transperineal approach during voiding. Studies are documented with static images and cine clips.

6. Intracavitary injection
   No standard US contrast agent dose or imaging protocol has been established for intracavitary applications. The reported dose range is 0.1 to 1.0 mL of SHLM contrast, 0.1 to 0.2 mL of PLM contrast, or 0.1 to 0.5 mL of PPM contrast diluted in 10 mL or greater of 0.9% normal saline. If scanning is performed using high-frequency US transducers, a higher concentration of contrast may be required for optimal visualization.

7. Interventional guidance
   a. Contrast Dose: The recommended dose of US contrast for interventional imaging is 2.4 mL of SHLM contrast, 0.2 mL of PLM contrast, or 1.0 mL of PPM contrast. Similar to other applications, the dose of the contrast material could be adjusted on the basis of the patient's body mass index, depth of the lesion, and transducer frequency.
      i. When performing interventional CEUS guidance, several injections of US contrast might be required.
      ii. The first bolus injection is used to identify the target lesion and plan the procedural approach.
      iii. The second bolus (or in some cases continuous contrast infusion) is used to guide biopsy needle placement.
      iv. When the target lesion begins to clearly appear after the second contrast injection (or infusion), the biopsy needle or ablation device is advanced into the target.
   b. Imaging
      i. In large/partially necrotic tumors, sampling should be performed on the basis of arterial-phase hyperenhancement of actively perfused viable tumor components.
      ii. In smaller lesions poorly seen on routine B-mode US imaging, the biopsy is performed in the late phase of CEUS imaging, targeting areas of tumor washout surrounded by actively perfused normal liver parenchyma.

Documentation

Accurate and complete documentation is essential for high-quality patient care. Written reports and US images/video clips that contain diagnostic information should be obtained and archived, with recommendations for follow-up studies if clinically applicable, in accordance with the *AIUM Practice Parameter for Documentation of an Ultrasound Examination*.

Equipment Specifications

The depth of penetration and image clarity may be reduced by low–mechanical index (MI) imaging. However, users should be aware that microbubble destruction can lead to artifactual or pseudo washout.

Image Acquisition

All CEUS studies should be performed on a machine with contrast imaging capability and a dual-display mode. Each vendor has different proprietary methods for optimal detection and display of CEUS. Regardless of the vendor, the modality and instrument settings that optimize visualization of contrast and opacification of vascular structures should be used. Most of these techniques use a real-time low-MI technique, usually less than 0.3 for continuous imaging. A high-MI mode may be chosen for rapid bubble destruction in the field of view to evaluate microbubble replenishment. The targeted lesion should be imaged with B-mode before the contrast study.

Contrast agent detection relies on harmonic imaging, and fundamental (nonharmonic) imaging should be avoided. Suppression of the background tissue signal by phase/amplitude modulation and harmonic techniques can increase the sensitivity of the machine to the CEUS signal, but strongly reflective structures may still create artifacts despite background suppression. Likewise, high doses of contrast may limit visualization of deeper structures; therefore, proper dosing of contrast is important.

Gain settings should be adjusted to reduce signals from background structures before contrast injection. The scan plane should be selected to avoid overlying shadowing structures. The focal zone is typically placed at the deepest portions of the region of concern (organ or lesion). For deeper lesions, a lower frequency is preferred for depth penetration and an optimized microbubble signal. If a higher frequency is selected, an increased volume of contrast may be necessary to achieve adequate contrast enhancement display, since the microbubble signal is higher at typical lower transducer frequencies, and a higher frequency may also result in faster loss of the microbubble volume because of bubble destruction.

Quality and Safety

Policies and procedures related to quality assurance and improvement, safety, infection control, and equipment performance monitoring should be developed

and implemented in accordance with the *AIUM Standards and Guidelines for the Accreditation of Ultrasound Practices*.

ALARA (As Low as Reasonably Achievable) Principle

The potential benefits and risks of each examination should be considered. The ALARA principle should be observed for factors that affect the acoustical output and by considering the transducer dwell time and total scanning time. Further details on ALARA may be found in the current AIUM publication Medical Ultrasound Safety.

Intravascular Administration

Mild physiologic adverse reactions include nausea and vomiting, taste alteration, headache, vertigo, flushing, and rash. These have an incidence of about 5%[15] and resolve spontaneously without lasting effects. Intra-arterial administration is contraindicated.

Ultrasound contrast agents (UCAs) are not contraindicated in patients with compromised renal function as they are not excreted by the kidneys. No blood tests are needed prior to administration.

1. Anaphylactoid (allergic-like) reactions

Ultrasound contrast agents carry an FDA black box warning and are contraindicated in patients with a history of allergy to the agent or its constituent gas or shell.

Hypersensitivity events are due to anaphylactoid (allergic-like) reactions to the gas or shell. Anaphylactoid reactions include hypotension with tachycardia, bronchospasm, urticaria, and pruritus. The incidence of serious anaphylactoid reactions is 0.006% to 0.01%,[16,17] which is comparable to gadolinium-based contrast agents and lower than that for iodinated contrast agents. The risk for these reactions may be increased among patients with unstable cardiopulmonary conditions. A rate of 0.001% has been reported for life-threatening anaphylactoid reactions, less than the rate for CT or MRI contrast agents.[18]

In most cases, hypersensitivity events occur within a few minutes of injection. Resuscitation equipment and trained personnel should be available when UCAs are administered. Contrast reactions should be managed according to the ACR Manual on Contrast Media Version 10.3 [19] and the ACR–SPR Practice Parameter for the Use of Intravascular Contrast Media.[20]

Ultrasound contrast agents have a similar safety profile in children.[21–23]

2. Intravesical and intracavitary administration

Mild physiologic adverse events during intravesical administration of UCAs in children have been reported in 0.8% to 3.8% of cases and are thought to be primarily related to bladder catheterization and not the UCA.[24,25]

Intracavitary administration of UCAs has not been associated with specific complications.

3. Pregnancy

There have been no studies of UCAs in pregnant patients for SHLM contrast or PLM contrast. Animal studies have shown no harm to the fetus at doses of SHLM contrast up to 8 to 17 times the human dose based on the body surface area.[26] There are no studies on PPM contrast in pregnant humans, but teratogenic effects have been demonstrated in animal studies. The FDA recommends that PPM contrast be used in pregnancy only if the benefit outweighs the risk.[27]

4. Breastfeeding

There are no data on the presence of UCAs in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's need for UCAs and any potential adverse effects on the breastfed infant from UCAs or from the underlying maternal condition. Milk can be pumped and discarded within 24 hours of contrast administration as a precautionary measure.

5. Bioeffects of bubble fragmentation

Ultrasound pulses at moderate and high MIs result in substantial microbubble oscillation and fragmentation, which are referred to as stable and inertial cavitation, respectively.[28] This microbubble oscillation can have a range of biological effects under certain conditions, ranging from short-term mild changes in cellular permeability at moderate MIs[29–31] to hemolysis and capillary endothelial injury at higher MIs.[32–34] The magnitude of cavitation is proportional to the

US amplitude[35] and inversely proportional to the frequency.

There have been reports of ventricular arrhythmias in echocardiography after imaging protocols that result in microbubble fragmentation when a high MI is applied.[36] However, no evidence of clinical bioeffects from cavitation during abdominal CEUS examinations have been found in humans at clinically relevant doses of contrast, and no cellular injury has been seen with CEUS examinations performed at the low power setting used in nondestructive imaging. However, given the evidence of bioeffects and that therapeutic applications of microbubbles are used with acoustic parameter ranges that have some overlap with diagnostic imaging parameters, microbubble insonation at moderate and high MIs should be used cautiously. The AIUM recommends that practitioners be aware of the MI used for any study, with an MI of 0.4 as a threshold value for bioeffects[37]:

"Induction of premature ventricular contractions, microvascular leakage with petechiae, glomerular capillary hemorrhage, and local cell killing in mammalian tissue in vivo have been reported and independently confirmed for diagnostic ultrasound exposure with a mechanical index (MI) above about 0.4 and a gas body contrast agent present in the circulation."

"Although the medical significance of such microscale bioeffects is uncertain, minimizing the potential for such effects represents prudent use of diagnostic ultrasound. In general, for imaging with contrast agents at an MI above 0.4, practitioners should use the minimal agent dose, MI, and examination time consistent with efficacious acquisition of diagnostic information."

Thus, an MI of greater than 0.4 for clearance pulses should be used sparingly and in accordance with the ALARA principle. Without a clearance pulse, contrast will usually be eliminated spontaneously from the circulation within 15 minutes.

Clinical CEUS examinations should generally be performed with a low MI of between 0.2 and 0.4.

PPM contrast contains human albumin, a derivative of human blood, and may confer a theoretical risk of viral or prion infection; additionally, it may not be used in patients with religious or ethical objections to the intravascular receipt of human blood products.

Infection Control

Transducer preparation, cleaning, and disinfection should follow manufacturer recommendations and be consistent with the *AIUM Guidelines for Cleaning and Preparing External- and Internal-Use Ultrasound Transducers Between Patients, Safe Handling, and Use of Ultrasound Coupling Gel*.

Equipment Performance Monitoring

Monitoring protocols for equipment performance should be developed and implemented in accordance with the *AIUM Standards and Guidelines for the Accreditation of Ultrasound Practices*.

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