ACR–AIUM–SPR–SRU PRACTICE PARAMETER FOR THE PERFORMANCE OF CONTRAST ENHANCED ULTRASOUND

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PREAMBLE

This document is an educational tool designed to assist practitioners in providing appropriate radiologic care for patients. Practice Parameters and Technical Standards are not inflexible rules or requirements of practice and are not intended, nor should they be used, to establish a legal standard of care[1]. For these reasons and those set forth below, the American College of Radiology and our collaborating medical specialty societies caution against the use of these documents in litigation in which the clinical decisions of a practitioner are called into question.

The ultimate judgment regarding the propriety of any specific procedure or course of action must be made by the practitioner considering all the circumstances presented. Thus, an approach that differs from the guidance in this document, standing alone, does not necessarily imply that the approach was below the standard of care. To the contrary, a conscientious practitioner may responsibly adopt a course of action different from that set forth in this document when, in the reasonable judgment of the practitioner, such course of action is indicated by variables such as the condition of the patient, limitations of available resources, or advances in knowledge or technology after publication of this document. However, a practitioner who employs an approach substantially different from the guidance in this document may consider documenting in the patient record information sufficient to explain the approach taken.

The practice of medicine involves the science, and the art of dealing with the prevention, diagnosis, alleviation, and treatment of disease. The variety and complexity of human conditions make it impossible to always reach the most appropriate diagnosis or to predict with certainty a particular response to treatment. Therefore, it should be recognized that adherence to the guidance in this document will not assure an accurate diagnosis or a successful outcome. All that should be expected is that the practitioner will follow a reasonable course of action based on current knowledge, available resources, and the needs of the patient to deliver effective and safe medical care. The purpose of this document is to assist practitioners in achieving this objective.

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1 *Iowa Medical Society and Iowa Society of Anesthesiologists v. Iowa Board of Nursing, 831 N.W.2d 826 (Iowa 2013) Iowa Supreme Court refuses to find that the "ACR Technical Standard for Management of the Use of Radiation in Fluoroscopic Procedures (Revised 2008)" sets a national standard for who may perform fluoroscopic procedures in light of the standard's stated purpose that ACR standards are educational tools and not intended to establish a legal standard of care. See also, Stanley v. McCarver, 63 P.3d 1076 (Ariz. App. 2003) where in a concurring opinion the Court stated that "published standards or guidelines of specialty medical organizations are useful in determining the duty owed or the standard of care applicable in a given situation" even though ACR standards themselves do not establish the standard of care.*

I. INTRODUCTION

The clinical aspects contained in specific sections of this practice parameter (Introduction, Specifications of the Examination, and Equipment Specifications) were developed collaboratively by the American College of Radiology (ACR), the American Institute of Ultrasound in Medicine (AIUM), the Society of Pediatric Radiology (SPR), and the Society of Radiologists in Ultrasound (SRU). Recommendations for Qualifications and Responsibilities of Personnel, Written Requests for the Examination, Documentation, and Quality Control and Improvement, Safety, Infection Control, and Patient Education vary among the three organizations and are addressed by each separately.

II. INDICATIONS

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

Ultrasound (US) contrast agents and contrast-specific scanning techniques have extended the diagnostic capabilities of US. CEUS should be considered as a useful problem-solving tool and as an indicated first-line imaging modality in select settings as indicated below.

US contrast has no renal toxicity or clearance; therefore, CEUS may be used at any level of renal function. CEUS is often safe for patients with contraindications to CT or MRI, including allergies to iodinated and gadolinium-based contrast material, claustrophobia, or immobility. Unlike CT, CEUS uses no ionizing radiation, which makes it particularly advantageous in pediatric patients. Additionally, sedation and/or general anesthesia are not required for patients who cannot comply with immobility or breath-hold instructions, including pediatric patients. CEUS may be performed without screening for incompatible metallic objects such as pacemakers, as is required for MRI.

II. INDICATIONS

A. Liver

1. Characterize focal liver lesions in the noncirrhotic adult liver or in the liver of a pediatric patient
    i. Further characterize incidentally found liver lesions on US
    ii. Evaluate incompletely characterized lesions on noncontrast or contrast enhanced CT or MRI
2. Characterize focal liver lesions in the cirrhotic liver
    i. Assess nodules detected on surveillance US
    ii. Assess LI-RADS (LR): LR-2, LR-3, LR-4, or LR-M observation on prior contrast enhanced CT or MRI
3. Detect arterial phase hyperenhancement when mistiming is suspected as the reason for its absence on prior CT or MRI
4. Detect washout not confidently seen on prior CT or MRI
5. Assess biopsied lesions with inconclusive histology
6. Follow up small observations, or observations not definitive for hepatocellular carcinoma for interval change
7. Detect metastases
8. Evaluate vasculature and portal pressures [1-6]
    i. Determine hepatic artery, portal vein, and hepatic vein patency
    ii. Assess transjugular intrahepatic portosystemic shunt patency
    iii. Distinguish bland thrombus versus tumor in vein
9. Guiding locoregional treatment of lesions that are poorly visualized on grayscale US
10. Assess residual viable disease following ablation or transarterial chemoembolization of hepatic malignancy.
11. Help select appropriate sites for biopsy by improving visualization of target and distinguishing viable (enhancing) from nonviable (nonenhancing) components

II. INDICATIONS

B. Kidney and Bladder

1. Intravenous Applications:
    i. Differentiate between renal tumors and anatomical variants mimicking a renal tumor
    ii. Differentiate cystic and solid renal masses
    iii. Characterize renal lesions based on complexity of features
    iv. Follow up nonsurgical renal lesions for change in size or other features
    v. Follow up for renal cancer recurrence following percutaneous ablation
    vi. Differentiate enhancing bladder neoplasm from non enhancing hematoma or other debris in patients with hematuria
    vii. Help select appropriate sites for biopsy by distinguishing viable (enhancing) from nonviable (nonenhancing) components.
    viii. Identify and guide for drainage of renal abscesses in complicated acute pyelonephritis
    ix. Improve diagnosis of renal artery stenosis or resolve vascular patency questions
    x. Assessment of native renal perfusion/cortical necrosis in the setting of acute renal failure
    xi. Evaluate transplant perfusion: infarct or ischemia
    xii. Evaluate transplant artery and vein patency
2. Intracavitary Applications:
    i. Pediatric contrast enhanced voiding urosonography
        - Evaluation of prenatally detected hydroureteronephrosis and urinary tract malformations
        - Diagnosis and follow-up vesicoureteral reflux
        - Characterize urethral abnormalities
        - Identification and characterization of urachal anomalies
    ii. Antegrade nephrostogram for evaluation of ureteral patency in the setting of indwelling nephrostomy tube [7]
    iii. Evaluate the presence and location of fistulae in anorectal malformations [8]: contrast enhanced genitosonography

3. Vessels
    a. Follow-up of endovascular aortic repair (EVAR) for the detection and classification of endoleaks
    b. Differentiate between total carotid and vertebral artery occlusion and residual flow through a tight stenosis

II. INDICATIONS

C. Pancreas

1. Differentiate vascular (solid) from avascular (eg, liquid or necrotic) components of a pancreatic lesion
2. Follow-up of indeterminate cystic pancreatic lesions
3. Improve the accuracy of percutaneous US-guided pancreatic procedures
4. Evaluate perfusion of pancreas transplant allograft [9]
5. Distinguish acute interstitial pancreatitis from necrotizing pancreatitis [10]

II. INDICATIONS

D. Bowel

1. Estimate disease activity in inflammatory bowel disease
2. Monitor the effect of treatment in Crohn's disease
3. Distinguish abscesses from inflammatory mass and improve visualization of fistulous tracks
4. Evaluate infants with suspected necrotizing enterocolitis for nonenhancing bowel

II. INDICATIONS

E. Spleen

1. Diagnose splenic infarction
2. Characterize indeterminate splenic lesions [11,12]

II. INDICATIONS

F. Scrotum

1. Distinguish vascularized masses from nonvascularized, nontumorous focal testicular lesions
2. Identify testicular infarction

II. INDICATIONS

G. Trauma

1. Evaluate for solid organ trauma
2. Evaluate for active bleeding
3. Evaluate for posttraumatic pseudoaneurysms

II. INDICATIONS

H. Intracaviatry injection

1. Identify needle or confirm catheter position, delineate any cavity or duct, improvetracking of fistulae.
2. Hysterosalpingography for confirming fallopian tube patency [13] [14,15]
3. Evaluate empyema complexity via chest tube injection [16]

II. INDICATIONS

I. Interventional guidance [17]

1. Avoid necrotic tissue to improve cytologic yield in the biopsy of tumors
2. Assist in identifying biopsy targets inconspicuous on noncontrast US or noncontrast CT
3. Assess for active bleeding after procedure

II. INDICATIONS

J. Other

1. Assess vascularized versus nonvascularized lesions in any other part of the body in addition to the organs listed
2. Intraoperative guidance and identification of resection margin [18]
3. Distinguish necrotic from nonnecrotic lung in pediatric pneumonia [16]
4. Distinguishcomplex from simple ovarian cysts
5. Distinguish gallbladder inspissated bile (tumefactive sludge) from vascularized soft tissue that may indicate neoplasm or focal adenomyomatosis [10]
6. Improve diagnostic performance of US in infant brain evaluation [19,20]
7. Evaluate neonatal brain hypoxic ischemic injury [21]

III. QUALIFICATIONS AND RESPONSIBILITIES OF PERSONNEL

See the ACR–SPR–SRU Practice Parameter for the Performance and Interpretation of Diagnostic Ultrasound Examinations [22].

An additional resource that may be helpful for training requirements is the European Federation of Societies for Ultrasound in Medicine and Biology CEUS Minimum Training Requirements for the Practice of Medical Ultrasound

in Europe [23].

Appropriate training and education are strongly advised for every operator who performs CEUS examinations. Furthermore, users should ensure that their US scanning machine is optimized for CEUS acquisition and the postprocessing of data. The operator must gain sufficient knowledge of indications and contraindications of CEUS and training in US contrast agent (UCA) administration and perform CEUS within the medicolegal framework.

IV. SPECIFICATIONS OF THE EXAMINATION

The written or electronic request for a contrast enhanced ultrasound examination should provide sufficient information to demonstrate the medical necessity of the examination and allow for its proper performance and interpretation.

Documentation that satisfies medical necessity includes 1) signs and symptoms and/or 2) relevant history (including known diagnoses). The provision of additional information regarding the specific reason for the examination or a provisional diagnosis would be helpful and may at times be needed to allow for the proper performance and interpretation of the examination.

The request for the examination must be originated by a physician or other appropriately licensed health care provider. The accompanying clinical information should be provided by a physician or other appropriately licensed health care provider familiar with the patient's clinical problem or question and consistent with the stated scope of practice requirements. (ACR Resolution 35, adopted in 2006 - revised in 2016, Resolution 12-b)

Depending on a state or institution's interpretation of the CMS rules of participation, a radiologist may add contrast to a "noncontrast" US order, depending on the indication for the study and/or findings identified during a routine US examination. Adding a same-day contrast study may decrease the time to final diagnosis and may decrease costs and harm by reducing unnecessary follow-up CT or MRI examinations [24].

Contrast Dose: In adults, the Food and Drug Administration (FDA) label dose for most abdominal applications is up to 2.4 mL of sulfur hexafluoride lipid microspheres (SHLM) contrast . However, the sensitivity to microbubble US contrast is substantially increased with modern equipment, and using a lower dose of 1–1.5 mL may be required to not saturate the image, limiting diagnostic accuracy. Larger doses may be needed when using high-frequency transducers and when imaging superficial structures or other tissues with low blood volume relative to liver or kidney. The half-life of SHLM contrast is relatively short (5 min), allowing multiple sequential injections. In children, the dose is 0.03 mL/kg up to a maximum of 2.4 mL per injection [25]. Intravascular administration of up to 5 mL of SHLM contrast in a single session is approved by the FDA.

The standard dose of perflutren lipid microspheres (PLM) contrast is 10 µL/kg. The standard dose of perflutren protein microspheres (PPM) contrast 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.

A 20-gauge (G) or larger venous line should be used to minimize microbubble destruction. Smaller lines may be used

when necessary, particularly in pediatric populations, with the minimum allowable size dependent on the type of microbubble. However, lines below 25G should generally be avoided. A 3-way stopcock attached to the venous line is often beneficial for minimizing time between contrast injection and subsequent saline flush. The contrast dose should be loaded along the straight bore of the stopcock, with a 5 or 10 cc saline syringe attached to the side bore. The rate of contrast injection varies between indications, but is often 1–2 cc/second followed by a 5–10 cc saline flush administered at the same rate [26]. Central venous lines and ports may be used following local and institutional guidelines and policies

IV. SPECIFICATIONS OF THE EXAMINATION

A. Summary of Scanning Protocols

1. General abdominal applications [27]

Most abdominal organs enhance rapidly and intensely 10–15 seconds after US contrast administration. The arterial vessels enhance first, followed by diffuse parenchymal enhancement. Contrast enhancement usually persists for 4–6 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. Imaging may be performed continuously or intermittently from contrast injection until the imaging target is expected to be completely enhanced (usually 60 seconds).
b. Thereafter, intermittent imaging (viewing for 3-5 seconds every 30-60 seconds) may be performed to evaluate washout.

IV. SPECIFICATIONS OF THE EXAMINATION

A. Summary of Scanning Protocols

2. Liver

Hepatic imaging protocol is based on the ACR CEUS LI-RADS recommendations.

a. CEUS of the liver is usually performed to assess targets clearly identified on precontrast B-mode imaging. CEUS may be limited in patients with high body mass index (BMI) and in patients with severe hepatic steatosis, mainly because of substantial US signal attenuation.
b. Contrast Dose: Contrast dose specified by the manufacturer should be used for the majority of examinations. Imaging of very superficial liver lesions with higher-frequency probes will require contrast dose increase. In addition to patient factors, the contrast dose can be adjusted down based on the sensitivity of the equipment used for CEUS examination [28,29].
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 one contrast injection and careful planning of patient positioning to maximize the use of limited acoustic windows. In patients with multiple liver nodules, two or three nodules can usually be imaged in one session.
e. The entire liver should be scanned after peak enhancement to detect areas of washout that may represent metastatic lesions.

IV. SPECIFICATIONS OF THE EXAMINATION

A. Summary of Scanning Protocols

3. Renal: Because of the highly vascular nature of the kidney, CEUS can be performed with less than the standard dose.

a. Imaging may be performed continuously or intermittently from contrast injection. Intermittent imaging (viewing for 3-5 seconds every 30-60 seconds) may be performed to evaluate washout, which is helpful to differentiate pseudo-masses from true neoplasms.
b. Lesion characterization often requires comparison to adjacent renal parenchyma. Therefore, ensuring a segment of parenchyma is within the field of view during the contrast injection is important for comparison with the target lesion.

IV. SPECIFICATIONS OF THE EXAMINATION

A. Summary of Scanning Protocols

4. Other abdominal applications [27]

IV. SPECIFICATIONS OF THE EXAMINATION

A. Summary of Scanning Protocols

5. EVAR and vascular

a. Contrast dose: CEUS examination of the aorta and great vessels is usually performed using a 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]) [30].
b. Imaging:
    i. Initial CEUS examination should focus on 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.

IV. SPECIFICATIONS OF THE EXAMINATION

A. Summary of Scanning Protocols

6. Scrotum

a. Contrast dose: 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. CEUS imaging should focus on the arterial phase because it is the most important aspect of the examination. Imaging should be performed continuously from contrast injection until the imaging target is adequately characterized. Presence and degree of arterial phase enhancement should be documented.

IV. SPECIFICATIONS OF THE EXAMINATION

A. Summary of Scanning Protocols

7. Neonatal brain [19-21,31]

a. Contrast dose: CEUS examination of the neonatal brain is performed using the standard pediatric weight-based dose of 0.03 mL/kg SHLM contrast.
b. Imaging:
    1. CEUS examination of the neonatal brain is performed with a small footprint curved-array mid-frequency transducer.
    2. CEUS is performed by saving cinematic clips.
    3. Once SHLM has been injected, care must be taken to only image in low mechanical index (MI), low TI, and low power output mode to avoid microbubble destruction and potential sonoporation. High MI pulses to clear the field should not be used.
    4. First, a wash-in cinematic clip is obtained in the coronal plane at the level of the third ventricle for 30 seconds after contrast injection. [20]
    5. Second, coronal anterior to posterior cinematic sweeps followed by right-to-left sagittal cinematic sweeps are saved to include both supratentorial and infratentorial structures.
    6. Finally, a cinematic sweep of the posterior fossa through the mastoid fontanelle is saved.
    7. Imaging may require more than one injection to visualize all relevant anatomy and pathology, depending on clinical indication.

IV. SPECIFICATIONS OF THE EXAMINATION

A. Summary of Scanning Protocols

8. Pediatric voiding urosonography [32,33]

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 is a 1-mL injection into a bladder that is partially filled with normal saline. However, a suspension of UCA and normal saline can also be infused into the bladder at a dose of approximately 0.2% of 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 due to frequent voiding and 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.

IV. SPECIFICATIONS OF THE EXAMINATION

A. Summary of Scanning Protocols

9. Intracavitary injection

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

IV. SPECIFICATIONS OF THE EXAMINATION

A. Summary of Scanning Protocols

10. Interventional guidance [17]

a. Contrast dose: Recommended dose of UCAs 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 contrast material could be adjusted based on patient's BMI, 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 can be used to identify the target lesion and plan the procedural approach.
    iii. The second bolus (or in some cases continuous contrast infusion) can be used to guide biopsy needle placement.
    iv. When the target lesion begins to clearly appear following the second contrast agent 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 based on arterial phase hyperenhancement of actively perfused viable tumor components.
    ii. In smaller lesions poorly seen on routine B-mode US, the biopsy is performed in the late phase of CEUS imaging, targeting areas of tumor washout surrounded by actively perfused normal liver parenchyma.

V. DOCUMENTATION

Reporting should be in accordance with the ACR Practice Parameter for Communication of Diagnostic Imaging Findings [34].

Adequate documentation is essential for high-quality patient care. There should be a permanent record of the US examination and its interpretation, including cine clips. Comparison with prior relevant imaging studies may prove helpful. Images of all appropriate areas, both normal and abnormal, should be recorded. Images should be labeled with the patient identification, facility identification, examination date, and image orientation. An official interpretation (final report) of the US examination should be included in the patient's medical record. Retention of

the US examination images should be consistent both with clinical need and with relevant legal and local health care facility requirements.

Data storage and access

All relevant images should be properly labeled to include the target and plane of imaging. The report or electronic medical record should include the type of contrast injected, number of injections, route, and dose. The relevant images should be stored digitally on a Picture Archiving and Communication System (PACS). The images should be readily available for review by all physician teams caring for the patient and making medical decisions based upon the results. Image storage should meet all local, state, and federal requirements for medical record document retention. Current and prior studies must be accessible in a reasonable timeframe for the clinical needs of the medical staff and the medical facility. See the ACR–AAPM–SIIM Technical Standard for Electronic Practice of Medical Imaging [35] for further details.

VI. EQUIPMENT SPECIFICATIONS

Equipment performance monitoring should be in accordance with the ACR–AAPM Technical Standard for Diagnostic Medical Physics Performance Monitoring of Real Time Ultrasound Equipment [36].

The depth of penetration and image clarity may be reduced by low MI imaging. However, using a higher MI can result in microbubble destruction. This generates strong echoes that can produce artifactual or pseudo-washout.

Image acquisition

All CEUS studies should be performed on a machine with contrast imaging capability and dual display mode. Each vendor has different proprietary methodology 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 employed. Most of these techniques use a real-time low MI technique, usually <0.2 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 upon nonlinear, contrast-specific imaging (most commonly variations of harmonic imaging), and fundamental (nonharmonic) imaging should be avoided. Suppression of background tissue signal by phase/amplitude modulation and harmonic techniques can increase the sensitivity of the machine to CEUS signal, but strongly reflective structures may still create artifact despite background suppression. Likewise, a high doses of contrast may limit visualization of deeper structures; therefore, proper dosing of contrast is important. For example, when evaluating the kidney with contrast, avoidance of a window that contains overlying spleen or liver will improve renal CEUS assessment.

Gain settings should be adjusted to reduce signal from background structures before CEUS injection. Scan plane should be selected to avoid overlying shadowing structures and keep the target lesion in the plane of imaging during quiet respiration. If the focal zone can be manually adjusted, it is typically placed at the deepest portions of the region of concern (organ or lesion). For deeper lesions, lower frequency is preferred for depth penetration and optimized microbubble signal. If higher frequency is selected, an increased volume of contrast may be necessary to achieve adequate contrast enhancement display because the microbubble signal is higher at typical lower transducer frequencies, closer to the microbubble volume resonance frequency. .

VII. QUALITY CONTROL AND IMPROVEMENT, SAFETY, INFECTION CONTROL, AND PATIENT EDUCATION

Policies and procedures related to quality, patient education, infection control, and safety should be developed and implemented in accordance with the ACR Policy on Quality Control and Improvement, Safety, Infection Control, and Patient Education appearing under the heading *Position Statement on QC & Improvement, Safety, Infection Control*, *and Patient Education* on the ACR website (https://www.acr.org/Advocacy-and-Economics/ACR-Position-Statements/Quality-Control-and-Improvement).

VII. QUALITY CONTROL AND IMPROVEMENT, SAFETY, INFECTION CONTROL, AND PATIENT EDUCATION

A. Intravascular administration

Mild physiologic adverse reactions include nausea and vomiting, taste alteration, headache, vertigo, flushing, and rash. These have an incidence of 0.2% [37-39] and resolve spontaneously without lasting effects.

US contrast agents (UCAs) are safe for patients with compromised renal function or renal obstruction because they are not excreted by the kidneys. No blood tests are needed before administration.

VII. QUALITY CONTROL AND IMPROVEMENT, SAFETY, INFECTION CONTROL, AND PATIENT EDUCATION

A. Intravascular administration

1. Anaphylactoid (allergic-like) reactions

UCAs carry an FDA black box [40] warning and are contraindicated in patients with a history of allergy to the agent or its components, such as polyethylene glycol.

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%–0.01% [38,41], 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 MR contrast agents [42].

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 [43] and the ACR–SPR Practice Parameter for the Use of Intravascular Contrast Media [44].

UCAs have a similar safety profile in children [45-47].

VII. QUALITY CONTROL AND IMPROVEMENT, SAFETY, INFECTION CONTROL, AND PATIENT EDUCATION

A. Intravascular administration

2. Intravesical and intracavitary administration

Mild physiologic adverse events during intravesical administration of UCAs in children have been reported in 0.8%–3.8% of cases and are thought to be primarily related to bladder catheterization and not the UCA [48,49].

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

VII. QUALITY CONTROL AND IMPROVEMENT, SAFETY, INFECTION CONTROL, AND PATIENT EDUCATION

A. Intravascular administration

3. Pregnancy

There have been limited studies of US contrast agents in pregnant patients for SHLM contrast or PLM contrast [50-54]. The limited literature suggests that using CEUS in pregnancy is safe; however, it should be documented that the use of CEUS is needed after a risk/benefit assessment. Animal studies have shown no harm to the fetus at doses of SHLM contrast up to 8–17 times the human dose based on body surface area [40,50]. 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 [55].

VII. QUALITY CONTROL AND IMPROVEMENT, SAFETY, INFECTION CONTROL, AND PATIENT EDUCATION

A. Intravascular administration

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 development and health benefits of breastfeeding should be considered along with the mother's need for UCAs and any potnetial 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.

VII. QUALITY CONTROL AND IMPROVEMENT, SAFETY, INFECTION CONTROL, AND PATIENT EDUCATION

A. Intravascular administration

5. Bioeffects of bubble fragmentation

US pulses at moderate and high mechanical indices result in substantial microbubble oscillation and fragmentation, which are referred to as stable and inertial cavitation, respectively [56]. This microbubble oscillation can have a range of biological effects under certain conditions, ranging from short-term mild changes in cellular permeability at moderate mechanical indices [57-59] to hemolysis and capillary endothelial injury at higher mechanical indices [60-62]. Early results on using these bioeffects to augment cancer treatments have been reported [63-65]. The magnitude of cavitation is proportional to US amplitude [66] and inversely proportional to frequency.

There have been reports of ventricular arrhythmias in echocardiography following imaging protocols that result in microbubble fragmentation when a high MI is applied [67]. However, no evidence of clinical bioeffects from cavitation during abdominal CEUS have been found in humans at clinically relevant doses of contrast, and no cellular injury has been seen with CEUS 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 mechanical indices 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 [68]:

> "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 US exposure with a 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 US. 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, MI above 0.4 for clearance pulses should be used sparingly and in accordance with the as low as reasonably achievable (ALARA) principle. Without a clearance pulse, contrast will usually be eliminated spontaneously from the circulation within 15 minutes.

Clinical CEUS should generally be performed with low MI imaging of 0.2 or less.

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.

VII. QUALITY CONTROL AND IMPROVEMENT, SAFETY, INFECTION CONTROL, AND PATIENT EDUCATION

A. Intravascular administration

6. Quality control

All US devices, including those performing CEUS studies, require annual acceptance testing by a trained, qualified

physicist and/or their designees. Routine annual quality control is also recommended. See the ACR–AAPM Technical Standard for Diagnostic Medical Physics Performance Monitoring of Real Time Ultrasound Equipment [36] for additional details.

ACKNOWLEDGEMENTS

This practice parameter was revised according to the process described under the heading *The Process for Developing ACR Practice Parameters and Technical Standards* on the ACR website (https://www.acr.org/Clinical-Resources/Practice-Parameters-and-Technical-Standards) by the Committee on Practice Parameters and Technical Standards of the ACR Commissions on Ultrasound and Pediatric Radiology in collaboration with the AIUM, the SPR, and the SRU.

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*Practice parameters and technical standards are published annually with an effective date of October 1 in the year in which amended, revised or approved by the ACR Council. For practice parameters and technical standards published before 1999, the effective date was January 1 following the year in which the practice parameter or technical standard was amended, revised, or approved by the ACR Council.

Development Chronology for this Practice Parameter

2019 (Resolution 25)
Revised 2023 (Resolution 33)