Guidelines for the Cardiac Sonographer in the Performance of Contrast Echocardiography: A Focused Update from the American Society of Echocardiography

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(J Am Soc Echocardiogr 2014;27:797-810.)

Keywords: Echocardiography, Sonographer, Contrast, Imaging

TABLE OF CONTENTS

In 2001, the American Society of Echocardiography (ASE) published a position paper that provided guidelines for the performance of contrast echocardiography by a sonographer.[1] The paper focused on the sonographer's role in four specific areas: understanding of microbubble physics and ultrasound instrumentation, recognition of indications for the use of contrast media, establishment of intravenous (IV) access privileges if necessary, and development of written policies for contrast agent infusion or injection.[1] It is the purpose of this paper to update sonographers on developments in these four areas and to provide useful tips that assist in optimizing the use of contrast media in an echocardiography laboratory. This will include the optimal use of both saline and left-sided contrast media, as well

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The following authors reported no actual or potential conflicts of interest in relation to this document: Sahar Abdelmoneim, MD, J. Todd Belcik, RCS, RDCS, FASE, Marti L. McCulloch, MBA, RDCS, FASE, Joan J. Olson, BS, RDCS, RVT, FASE, Charlene Porcelli, BS, RDCS, RDMS, FASE, Jeane M. Tsutsui, MD, and Kevin Wei, MD, FASE. The following authors reported relationships with one or more commercial interests: Sharon L. Mulvagh, MD, FASE, receives research support from Lantheus Medical Imaging and Astellas Pharma. Thomas R. Porter, MD, FASE, has received research support from Philips Research North America, GE Healthcare, Astellas Pharma, and Lantheus Medical Imaging.

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0894-7317/$36.00

http://dx.doi.org/10.1016/j.echo.2014.05.011

Abbreviations

AMI = Acute myocardial infarction

ASE = American Society of Echocardiography

CP = Chest pain

FDA = US Food and Drug Administration

IAC = Intersocietal Accreditation Commission

IV = Intravenous

LV = Left ventricular

LVO = Left ventricular opacification

MI = Mechanical index

PFO = Patent foramen ovale

PHT = Pulmonary hypertension

RVSP = Right ventricular systolic pressure

TEE = Transesophageal echocardiography

TTE = Transthoracic echocardiography

UCA = Ultrasound contrast agent

as safety information and recommended policies for left-sided contrast agent use.

I. UPDATE ON KNOWLEDGE OF ULTRASOUND PHYSICS AND INSTRUMENTATION

Since the 2001 document, considerable progress has been made in the area of improving the visualization of a commercially available ultrasound contrast agent (UCA) for left ventricular (LV) opacification (LVO) and perfusion. With regard to details on the composition of commercially available microbubbles and microbubble physics, please refer to the "Contrast Agents" and "Contrast-Specific Ultrasound Imaging" sections in the 2008 ASE consensus statement.[2] Contrast enhancement for LVO using low–mechanical index (MI) harmonic imaging has been available on all ultrasound systems marketed within the past decade, and real-time very low MI techniques are available on nearly all commercially available systems. By definition, very low MI represents values < 0.2, low MI represents values < 0.3, intermediate MI represents values of 0.3 to 0.5, and high MI is any MI that exceeds 0.5. The real-time very low MI techniques permit the enhanced detection of microbubbles within the LV cavity and myocardium.[2] Although myocardial perfusion imaging is not an approved indication for UCAs, these very low MI imaging techniques have been used in multiple clinical studies to examine perfusion and improve the detection of coronary artery disease in the emergency department, improve the detection of coronary artery disease during stress testing, and improve the diagnostic evaluation of cardiac masses. Therefore, sonographers should be familiar with the advantages and drawbacks of each contrast imaging method (Table 1) and the physics related to each technique (Figure 1).

Pulse-inversion Doppler (originally developed by Advanced Technology Laboratories, now used by GE Healthcare, Little Chalfont, United Kingdom) is a tissue cancelation technique that overcomes motion artifacts by sending multiple pulses of alternating polarity into the cavity and myocardium. Although pulse-inversion Doppler provides excellent tissue suppression and high resolution by receiving only even-order harmonics, there is significant attenuation, especially in the basal myocardial segments of apical windows. **Power modulation** (originally developed by Philips Medical Systems, Andover, MA) is a technique that improves the signal-to-noise ratio at very low MIs (0.05–0.20). This technique is also a multipulse cancelation technique, only here, the power, or amplitude, of each pulse is varied. The low-power pulses create a linear response, whereas the slightly higher power pulse results in a linear response from tissue but a nonlinear response from microbubbles. The linear responses from the two different pulses (the amplified low-power pulse and the slightly higher power pulse) can be subtracted from each other. The transducer then only detects the nonlinear behavior, which emanates exclusively from the microbubbles. Power modulation also detects fundamental nonlinear behavior but does not have the resolution and image quality that pulse inversion offers. **Contrast pulse sequencing** (originally developed by Siemens Medical Solutions USA, Mountain View, CA) combines these multipulse techniques by interpulse phase and amplitude modulation, which although more complex has the purpose of enhancing nonlinear activity from microbubbles at a low MI and canceling out the linear responses from tissue. Contrast imaging with each specific pulse-sequence scheme can be used at very low MIs (<0.2) to assess LVO and myocardial contrast perfusion in real time with excellent spatial resolution. Sonographers should be aware of the variations in pulse-sequence schemes and use them if available whenever contrast is required (Table 1). The advantage, compared with B-mode low-MI harmonic imaging (LVO), is that there is better tissue cancelation and enhanced contrast from microbubbles. However, not all vendors have real-time very low MI imaging software available, and in these settings, low-MI (<0.3) harmonic imaging should be used.

This document provides instructions on how to set up very low MI real-time imaging, and the video examples provide specific examples as well as potential artifacts. The writing group recommends that sonographers who are just beginning to use UCAs, or who do not have very low MI imaging software available, start with the low-MI harmonic imaging methods described in Table 1. We recognize that experience is a critical factor in performing any aspect of ultrasound imaging, and we recommend to all sites that they work with their local contrast agent representatives to optimize contrast with low-MI imaging techniques and with their specific ultrasound vendors on how to effectively use real-time very low MI imaging software.

II. UPDATE ON CONTRAST ADMINISTRATION POLICY AND ESTABLISHING INTRAVENOUS ACCESS

It is recognized that the establishment of IV access remains one of the biggest obstacles to administering UCAs in clinical echocardiography laboratories. Because UCAs are critical to improving the detection of regional wall motion abnormalities and improving the detection of Doppler signals, it is essential that sonographers work with hospital administrations to adopt a contrast program that promotes their use in technically difficult studies. In August 2012, the Intersocietal Accreditation Commission (IAC) officially released the new IAC standards and guidelines for adult echocardiography accreditation.[3] The guidelines require all cardiac ultrasound systems to have instrument settings to enable the optimization of UCAs. The IAC guidelines recommend using UCAs for all studies with suboptimal image quality and require a policy or process to enable alternative imaging for suboptimal studies. Several large clinically active cardiology programs have put in place policies for UCA use that assist sonographers in complying with current IAC guidelines. This update reemphasizes the 2001 statement that the ASE supports IV training for sonographers in hospital and clinic settings. This training requires knowledge of aseptic technique, venous anatomy, appropriate sites of access, risks to patients, and hospital approval to perform the technique. To

Table 1 Comparison of different low-MI imaging techniques

Descriptor	Company Manufacturer(s)	Tissue cancelation technique	Advantage(s)	Disadvantage(s)
Pulse-inversion Doppler and very low MI*	Philips Sonos/iE33 Toshiba Aplio/Xario GE 1.5-, 1.6-, and 1.7-MHz transducers	Alternating polarity	High resolution	Attenuation and dynamic range
Power modulation and very low MI*	Philips Sonos/iE33 GE 2.1- and 2.4-MHz transducers	Alternating amplitude	High sensitivity	Resolution, image quality, and dynamic range
Contrast pulse sequencing and very low MI*	Siemens Acuson	Both alternating polarity and alternating amplitude	Image quality and high sensitivity	Attenuation and dynamic range
Low-MI† harmonic (LVO)	All vendors	B-mode; no cancelation	Image quality	Decreased contrast sensitivity, apical swirling, and no perfusion

*Very low MI, <0.2.
†Low MI, <0.3.

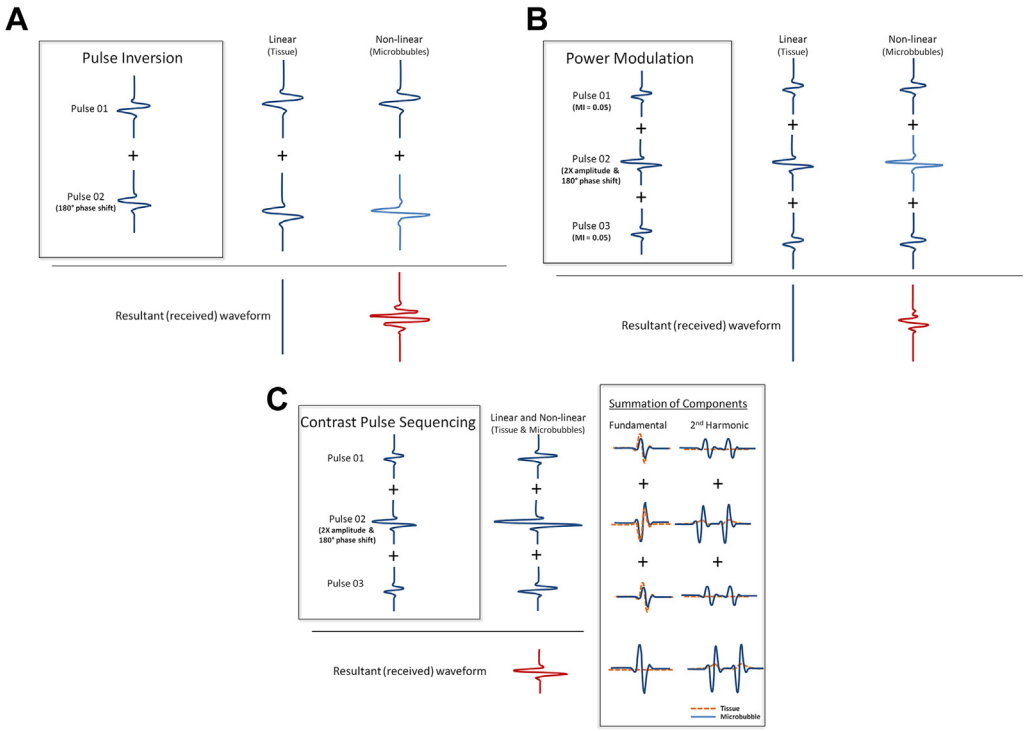

Figure 1 Demonstration of the different tissue cancelation techniques used with very low MI imaging to enhance microbubble contrast and eliminate tissue signals.

optimize echocardiographic quality and improve patient care by reducing unnecessary additional procedures, UCAs should be used when indicated, and sonographers deserve full hospital administrative support in achieving this IAC mandate. The Appendix describes the different methods by which hospitals have developed contrast protocols that permit the streamlined use of UCAs while minimally affecting hospital throughput.

III. UPDATE ON HOW AND WHEN TO PERFORM CONTRAST ECHOCARDIOGRAPHY

UCAs should be used whenever suboptimal images exist for the quantification of chamber volumes and ejection fraction and the assessment of regional wall motion (see Table 3 of the ASE consensus statement[2]). Suboptimal images are defined as the inability to detect two or more contiguous segments in any three of the apical windows. Doppler flow evaluations with UCAs should be performed on rest or stress studies if spectral signals to quantify velocities and pressure gradients were inadequate. Doppler enhancement with UCAs can be done in the same studies in which UCAs were used to improve LVO.

The writing group recommends that users become familiar with both the bolus techniques and continuous infusion methods described in the Appendix. Bolus injections can result in severe attenuation of the LV cavity, which takes time to resolve. If a bolus is to be used, it is recommended to give it as a 0.5-mL dose of a dilution of Definity (Lantheus Medical Imaging, North Billerica, MA) (one vial in 8.5 mL of saline) or as a 0.3-mL dose of undiluted Optison (GE

Table 2 Common problems and artifacts encountered when using IV contrast

Typical location of artifact	Artifact/problem	Sonographer correction method	Key additional points
Apex-endocardial border	Swirling	Use real-time very low MI imaging Increase contrast infusion rate (Video 7; available at www.onlinejase.com)	Lower frame rate prevents apical destruction; also can move focus to near field.
Apex-myocardium	Reduced contrast	Increase near-field TGC under resting conditions; move focus temporarily to near field (Video 8; available at www.onlinejase.com)	If resting wall motion is normal, perfusion should be normal, so a defect in this setting is an artifact.
Basal segment–myocardium	Reduced myocardial contrast	Additional foreshortened apical windows to get basal segments in the near field (Video 9; available at www.onlinejase.com)	If resting wall motion is normal, perfusion is normal, and therefore there should be no resting contrast defects in the absence of wall motion abnormalities. Use this concept in setting up receiver gain during resting images, because during stress, perfusion alone can be abnormal.
LV cavity contrast	Inadequate using a continuous infusion	Check IV site to ensure not obstructed; increase infusion rate; ensure contrast is not too dilute and is staying adequately mixed	Could switch to a small bolus.
LV cavity contrast	Shadowing of basal/mid segments	Slow down infusion or reduce bolus size and flush rate	Infusion (compared with bolus) reduces shadowing problems and allows more rapid correction of the problem.

TGC, Time gain compensation.

Table 3 Specific interventions during agitated saline injection designed to increase right atrial contrast and improve the detection of a PFO

Maneuver(s)	Specific intervention/timing	Mechanism
Add blood	10% blood added to 10% air and 80% saline	Produces smaller, more concentrated microbubbles
Cough, Valsalva maneuver, and abdominal compression	Performed during full RA opacification	Transiently increases RA pressure, creating RA-to-LA pressure gradient
Femoral vein injection	Performed instead of arm injection	IVC flow is directed to the IAS; SVC flow is directed to the TV

IAS, Interatrial septum; *IVC*, inferior vena cava; *LA*, left atrial; *RA*, right atrial; *SVC*, superior vena cava; *TV*, tricuspid valve.

Healthcare, Little Chalfont, United Kingdom). In each case, the saline flush should be approximately 3 mL over 10 sec. Depending on the indication for contrast agent use, the sonographer should optimize the MI to improve detection of contrast agent in specific areas. Contrast agent administration should be done with either harmonic low-MI imaging or with the very low MI real-time software described in Table 1, not with fundamental imaging. The Appendix describes the administration techniques used by the different members of the writing group for both bolus injections and continuous infusions. In general, low-MI harmonic imaging requires lowering the MI to <0.3 while in a harmonic imaging mode and the administration of small boluses (as described above) followed by slow saline flushes (3–5 mL over 5–10 sec). The very low MI real-time imaging techniques are inherently tissue cancelation techniques that eliminate or reduce myocardial and valvular signals in the absence of contrast. Brief (three to 10 frames) high-MI "flashes" can be used to clear contrast from the myocardium or from intracardiac masses, to analyze the rate at which contrast replenishes these areas. Normal resting myocardial contrast replenishment should occur within 4 sec, while during stress imaging, the replenishment should occur within 2 sec (see Section V). The time gain compensation settings should be adjusted under resting conditions so that myocardial and LVO appears even from the base to the apex, which typically requires a slight adjustment upward of the near-field potentiometers (or near-field time gain compensation settings). Specific setups for sonographers in different clinical settings are described below. The ASE's ContrastZone Web site (http://www.contrastzone.com) has additional tips and instructions for using contrast to improve LVO.

LV Ejection Fraction and Regional Wall Motion Assessment

This clinical setting includes both situations in which accurate serial assessments of ejection fraction are required (e.g., chemotherapy) and when visualization of the endocardium is critical (evaluation of chest pain [CP] or during stress echocardiography). In this context, a contrast infusion or slow bolus/flush technique should be used to ensure optimal LVO without shadowing of basal segments or swirling

of contrast agent in the apical portion of the LV cavity. Swirling can be avoided by using the real-time very low MI techniques or using a lower scan-line density in the near field with low-MI harmonic imaging. Multicenter studies have emphasized the use of a low MI (<0.3) to achieve full opacification of the apex to optimize the detection of regional wall motion abnormalities and quantify ejection fraction.[4] It is recommended that both regional wall motion analysis and quantification of volumes not be made until full opacification of the left ventricle is achieved without apical swirling or basal segment attenuation. Although perfusion imaging is not an approved indication, the detection of myocardial contrast enhancement after brief high-MI impulses does correlate with myocardial blood flow abnormalities and may improve the detection of subendocardial wall motion abnormalities using the same infusion or slow bolus/flush techniques used to optimize LVO.[2]

Hypertrophic Cardiomyopathy, Apical Variant

The apical variant of hypertrophy associated with hypertrophic cardiomyopathy is present in about 7% of affected patients but may not be detected by routine surface echocardiography, because of incomplete visualization of the apical endocardial border.[2] When apical hypertrophic cardiomyopathy is suspected but not clearly documented or excluded, contrast studies should be performed. If apical hypertrophic cardiomyopathy is present, the characteristic spadelike appearance of the LV cavity, with marked apical myocardial wall thickening, is clearly evident on contrast-enhanced images.[5]

LV Noncompaction

Noncompaction of the myocardium is an uncommon but increasingly recognized abnormality that can lead to heart failure and death.[2] It is due to alterations of myocardial structure with thickened, hypokinetic segments that consist of two layers: a thin, compacted subepicardial myocardium and a thicker, noncompacted subendocardial myocardium. When LV noncompaction is suspected but inadequately visualized with conventional two-dimensional imaging, the characteristic deep intertrabecular recesses of the noncompacted layer may be identified by showing contrast medium–filled intracavitary blood between prominent LV trabeculations.[6] In this setting, it is recommended that one use a harmonic MI setting that is intermediate (i.e., 0.3–0.5) rather than the usual low-MI imaging, to more clearly delineate the trabeculations (Video 1; available at www.onlinejase.com). Although several different diagnostic criteria are used to diagnose isolated noncompaction, the writing group recommends a noncompacted to compacted ratio of >2:1 when using contrast.

LV Thrombus and Intracardiac Mass Evaluation

LV thrombi are most commonly located in the LV apex.[2] An apical thrombus may be difficult to define clearly, or to exclude, especially if the apex is foreshortened or there is near-field ring-down artifact. The use of UCAs reduces the likelihood of foreshortening of the left ventricle, enabling full visualization of the apex and detection of the telltale "filling defect" sign of a thrombus, which might otherwise be missed.[7] In a recent study of patients at high risk for thrombus because of myocardial infarction or heart failure, contrast echocardiography nearly doubled the sensitivity (61% vs 33%, $P < .05$) and yielded improved accuracy (92% vs 82%, $P < .01$) compared with noncontrast echocardiography for the detection of LV thrombi, of which 75% were apical.[8] In that study, contrast echocardiography and cine magnetic resonance imaging closely agreed on the diagnosis of thrombus ($\kappa = 0.79$, $P < .001$), although thrombus prevalence was lower by contrast echocardiography than delayed-enhancement cardiac magnetic resonance ($P < .05$). Those thrombi that were detected by delayed-enhancement cardiac magnetic resonance, but not by contrast echocardiography, were more likely to be mural in shape or small in volume ($P < .05$). The writing group recommends that ultrasound contrast agent be used to assess for cavitary thrombi whenever the LV apex is not clearly visualized on a noncontrast examination of a patient with severely depressed systolic function.

To differentiate a thrombus from an intracardiac tumor, real-time very low MI perfusion imaging with high-MI flash should be used if available.[9] Thrombi are avascular and show no contrast enhancement after a high-MI flash impulse, as opposed to tumors, which may be either poorly (benign stromal tumors, such as myxoma) or highly (malignant tumors) vascularized and will demonstrate proportional degrees of perfusion by flash replenishment real-time very low MI imaging (Videos 2-4; available at www.onlinejase.com). If real-time very low MI software is not available, low-MI (<0.3) harmonic imaging can be deployed to visualize whether contrast enhancement is occurring within the mass and aid in the differentiation of cardiac masses.

LV Aneurysm versus Pseudoaneurysm

LV aneurysm, an often asymptomatic complication of a prior myocardial infarction, is the most common LV apical abnormality.[2] It is characterized by thin walls and a dilated apex, which may be akinetic or dyskinetic. These findings are usually easily visualized with echocardiographic imaging. However, if the apex is foreshortened and not completely visualized, an apical aneurysm may go undetected. UCAs can aid in visualizing apical wall motion abnormalities, but care must still be taken to minimize foreshortening. In addition, associated abnormalities (such as LV apical thrombus) may not be visible until a UCA is used. The use of UCAs by a sonographer to detect an apical aneurysm or a thrombus also requires the use of both the parasternal and apical windows to delineate the extent of the abnormality and avoid foreshortening. Similarly, a pseudoaneurysm can be distinguished from an aneurysm using contrast to demonstrate a narrow neck and systolic filling of the pseudoaneurysm sac.[10] (Video 5; available at www.onlinejase.com) demonstrates examples of contrast filling an apical and inferior pseudoaneurysms in systole. Both cases were confirmed at surgery.

Other Less Common Apical Abnormalities

The characteristic layering of thrombus and necrotic material at one or both of the left and right ventricular apices, without underlying wall motion abnormality and preserved perfusion with contrast, can be seen in endomyocardial fibrosis (Figure 2).

Stress-induced (takotsubo) cardiomyopathy most frequently affects the mid to apical region of the left ventricle, in a distribution that is not characteristic of coronary artery disease (Figure 3). The classic appearance of the left ventricle in this disorder is more fully characterized and appreciated when the left ventricle is opacified with contrast agent.[11] Moreover, delayed, but present, myocardial perfusion in the affected segments may help differentiate stress-induced cardiomyopathy from epicardial coronary disease. This is a critical diagnostic finding, especially in postmenopausal women presenting with acute coronary syndromes, who not infrequently have associated renal dysfunction or other relative contraindications for angiography.[11]

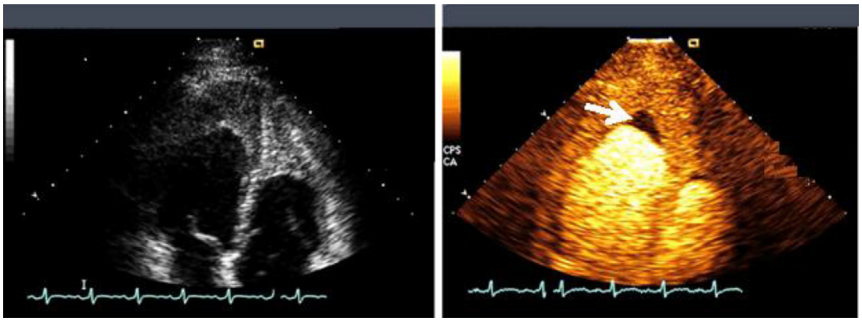

Figure 2 Noncontrast (*left*) and real-time very low MI contrast-enhanced (*right*) images of a patient with an apical mass in whom real-time very low MI imaging delineates both perfusion and nonperfusion due to endomyocardial fibrosis with thrombus formation (*arrow*).

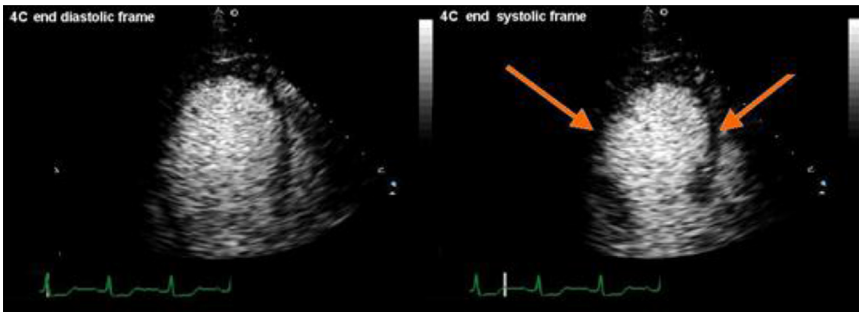

Figure 3 Contrast-enhanced LV cavity to assist in delineating the extensive apical wall motion abnormality (*arrows*) associated with takotsubo syndrome. End-diastolic image is on the left and end-systolic image on the right. This is a reverse four-chamber view, and hence the left ventricle is on the left side of the image.

Emergency Department CP Evaluation

Acute CP is one of the most common presenting symptoms to an emergency department. The causes of this symptom may range from benign musculoskeletal problems to life-threatening conditions such as acute myocardial infarction (AMI), aortic dissection, or acute pulmonary embolism. Of these "serious" causes of CP, AMI occurs the most frequently.[12,13] Making an early diagnosis of AMI, however, can be difficult, because the medical history, physical examination, electrocardiography, and chest radiography all have poor sensitivity. Serum cardiac biomarkers are currently the main methods used to determine if a patient is presenting with an AMI, but they are not released into the serum until hours after the onset of symptoms.[14] Echocardiography can be used to detect a patient with an acute coronary syndrome because even after a brief coronary occlusion (5–15 min), regional systolic function is reduced.[15] More important, the absence of a segmental wall thickening abnormality can exclude an ischemic cause of CP. Normal regional function identifies a low-risk population with a 24-hour adverse event rate of only 0.4%.[16] Patients with abnormal regional function are sixfold more likely to have early events compared with those with normal function.[17,18]

Therefore, for sonographers, the use of UCAs in patients with CP is critical to attain optimal sensitivity for detecting even small focal wall thickening abnormalities. The use of UCAs has been shown to significantly improve the detection of a new segmental abnormality.[11,19] It is the sonographer's role to quickly evaluate *all* LV wall segments in patients with suspected acute coronary syndromes; however, this must be done with the mind-set that if two contiguous wall segments cannot be visualized, wall motion must be further evaluated with the use of UCAs. An example of a lateral wall motion abnormality detected only with very low MI contrast imaging is demonstrated in (Video 6; available at www.onlinejase.com). The use of real-time very low MI imaging in patients with CP adds additional diagnostic and prognostic information by simultaneously providing perfusion information. If complete replenishment of contrast is observed within 4 sec in a segment with abnormal regional wall motion (i.e., normal perfusion), this identifies a patient at intermediate risk for cardiac events compared with a high-risk situation in which both a regional perfusion abnormality (delayed replenishment of contrast) and a wall motion abnormality exist.[16,17]

IV. UPDATE ON CONTRAST INJECTION AND INFUSION SAFETY

One of the most significant developments since the original sonographer contrast guidelines were published was the issuance of a black-box warning by the US Food and Drug Administration (FDA) on Optison and Definity in October 2007 and a subsequent series of labeling revisions. The warning initially recommended that patients at high risk for or with pulmonary hypertension (PHT) or unstable cardiopulmonary conditions be closely monitored until 30 min after receiving UCA injections. The FDA also required manufacturers to conduct additional prospective clinical studies evaluating the safety of the approved UCAs and their effects on pulmonary hemodynamics in patients with and without PHT. Since this warning was issued, there have been a series of publications confirming the safety of both Optison and Definity.[20-23] Several contraindications were removed from Definity and Optison in May 2008, although the

label revisions still required physiologic monitoring for patients with PHT and unstable cardiopulmonary syndromes. These monitoring requirements for PHT and unstable cardiopulmonary syndromes were also removed in 2011 after the completion of safety studies in this specific setting (see below). In addition, a statement indicating that the usefulness and safety of UCAs had not been demonstrated in stress echocardiography was removed, thus implying usefulness and safety during stress testing.

The current FDA labeling is as follows: "Serious cardiopulmonary reactions, including fatalities, have occurred uncommonly during or following perflutren-containing microsphere administration. Most serious reactions occur within 30 minutes of administration. Assess all patients for the presence of any condition that precludes Definity/Optison administration. Always have resuscitation equipment and trained personnel readily available." The current contraindications to contrast are (1) right-to-left, bidirectional, or transient right-to-left cardiac shunts; (2) hypersensitivity to perflutren; and (3) hypersensitivity to blood, blood products, or albumin (in the case of Optison only).

A consensus of the writing group, based on a review of several thousand patients receiving Definity or Optison contrast,[20-23] is that the life-threatening reactions are rare (<1 in 10,000) and that this residual warning should not be considered an excuse to withhold contrast. On the basis of this combined large patient database, there is sufficient evidence to believe that UCAs have a high benefit-to-risk ratio and certainly less risk than other commonly used contrast agents in other imaging modalities.

Anaphylactic Reaction Response Protocols

Although anaphylactoid reactions to UCAs are rare, it is advised that a sonographer, in conjunction with nurses and physicians in the echocardiography lab, develop a policy for early recognition and effective management of these acute life-threatening reactions. The purpose of the policy is to outline the process for activation, determination, and implementation of the roles of team members involved in an acute allergic reaction to UCAs. Cardiopulmonary resuscitation personnel and equipment should be readily available before UCA administration, and all patients should be monitored for acute reactions. Allergy kits should be readily available in all echocardiography labs that administer UCAs. The kits ought to be placed in areas where contrast materials are frequently administered. The nurses or designated medical personnel should be in charge of maintaining the kits and performing monthly checks for expiration dates. Once an allergic reaction is identified, the nurse should assess the patient and initiate treatment on the basis of the symptoms and immediately notify the supervising physician. Depending on the severity of the anaphylactic reaction, assistance of the rapid-response team or code team may be required. Although respiratory distress due to bronchospasm is the most serious concern, other reactions include shock; urticarial, facial, or laryngeal edema; seizures; and convulsions.

Although back pain is a more common side effect with Definity, the actual cause for this is still speculative and under investigation. The leading hypothesis is that it is related to a complement-mediated idiosyncratic reaction, which can also be observed with other injectable agents containing lipid membranes. If back pain occurs during UCA administration, discontinue injection and monitor vital signs. No further treatment is needed, and in most cases the pain resolves spontaneously within a few minutes. If contrast is needed again in patients who have experienced back pain with Definity, an alternative contrast agent such as Optison should be used.

Use of Ultrasound Contrast Agents in PHT

The FDA had initially considered PHT as a contraindication for IV UCAs. This was based on early studies demonstrating that unshelled microbubbles administered intravenously could result in progressive drops in arterial saturation, cardiac output, and stroke volume, with increases in pulmonary vascular resistance and pulmonary artery pressure. The current UCAs approved by the FDA are composed of high–molecular weight gases and various types of shells that remain relatively stable in circulation and for the most part are $<10\ \mu m$. Several retrospective and prospective studies have focused on the effects of UCAs on pulmonary hemodynamics and safety.[23-26] A phase 4, open label, nonrandomized, multicenter study evaluated the effects of Definity in patients with normal (<35 mm Hg) or elevated right ventricular systolic pressure (RVSP; >35 mm Hg). There were no significant changes in either pulmonary or systemic hemodynamics in control subjects or in subjects with elevated RVSP after a slow bolus administration of Definity (10 μL/kg) over 30 to 60 sec, followed by a 10-mL saline flush.[24] A large multicenter study of 1,513 patients receiving Definity contrast (mean age, 69 ± 14 years; 55% men), of whom 911 (60%) had mild PHT, 515 (34%) had moderate PHT, and 87 (6%) had severe PHT, demonstrated that adverse events were rare (0.002%) and for the most part not attributable to Definity.[25] One of the largest retrospective cohort examined 1,900 subjects with RVSP ≥ 35 mm Hg, 414 (7%) with RVSP ≥ 50 mm Hg, and 118 (2%) with RVSP ≥ 60 mm Hg. The study found no increase in the rate of myocardial infarction or death during either short-term (≤72 hours) or long-term (≤30 days) follow-up (Figure 4). Additionally, there was no association between the incidence of contrast-related side effects and RVSP.[26]

After completion of the pulmonary hemodynamic studies showing no significant untoward effects, further revision to the black-box warning occurred in October 2011, including removal of statements requiring monitoring of patients with PHT. From the sonographer's perspective, contrast agents can be helpful in patients with PHT by improving the evaluation of regional right ventricular wall motion,[27] but contrast media must be given at lower infusion rates so as not to cause right ventricular shadowing. Contrast agents are also helpful for improving Doppler image quality,[2] especially the tricuspid regurgitant jet that is used to estimate pulmonary artery systolic pressure. The Doppler gain settings should be lowered for this application, to reduce background noise. On the basis of these data, the writing group recommends that if a contrast agent is needed to improve right ventricular opacification or LVO or Doppler enhancement in a patient with PHT, it should be used.

Safety in Patients with Patent Foramen Ovale and Congenital Heart Diseases

According to the FDA, right-to-left shunting is a contraindication to UCA use. However, patent foramen ovale (PFO) is very common, with prevalence rates of up to 35%.[27] Recent large reviews of the literature have failed to detect any increased risk for systemic embolization associated with UCAs in patient populations that obviously included those with PFOs.[28] Therefore, the writing group does not consider patients with small degrees of right-to-left shunting through PFOs (those that result in a transient appearance of saline contrast in the left atrium or ventricle and do not fill the left atrial or LV cavity) at increased risk for UCA use.

In the setting of corrected or uncorrected congenital heart disease, there is emerging evidence that contrast may be safe and useful in evaluating regional right ventricular and LV regional wall motion

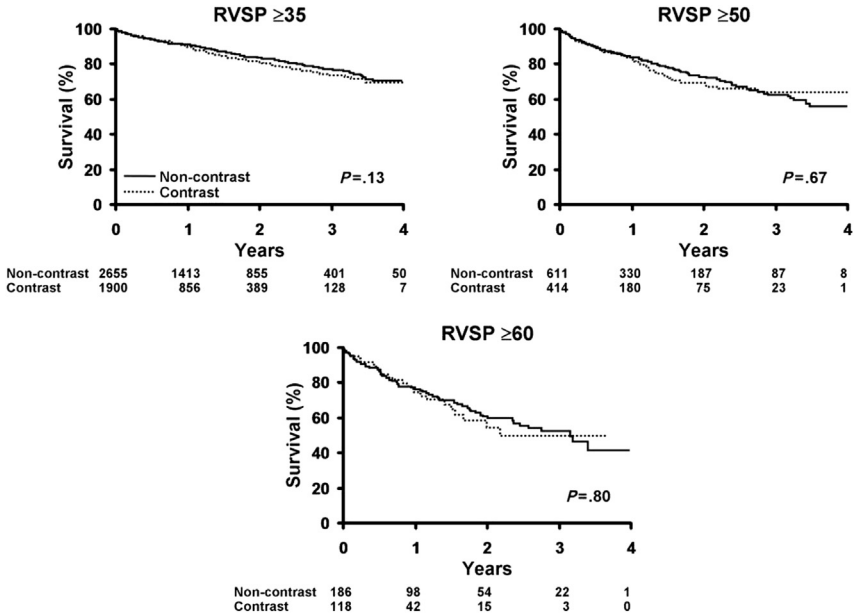

Figure 4 Short- and long-term outcomes after both IV Optison and Definity injections in patients with varying severity of PHT. Note no difference in survival compared with a control group with equivalent pressures who did not receive UCAs. Reproduced with permission from Abdelmoneim *et al*.[26]

and perfusion.[29] Although no pediatric indications exist yet for contrast, contrast should be considered in adults with corrected or uncorrected congenital heart disease if needed, as long as a large right-to-left shunt does not exist.

V. KEY COMPONENTS FOR OPTIMIZING THE CONTRAST EXAMINATION

To ensure optimal use of UCAs, a very low MI (<0.2) combined with vendor-specific modalities that optimize contrast opacification should be used. The real-time very low MI packages available to Philips, Siemens Acuson, Toshiba, and GE users permit full LVO in real time without encountering artifacts created by apical swirling. Therefore, if available, the sonographer should begin UCA administration for assessment of LV endocardial border definition using a real-time very low MI imaging modality. If real-time very low MI imaging is not available, using standard harmonic imaging at a low MI (<0.3) is still effective but may require more contrast to achieve full opacification. It is important that the sonographer place the focus at the level of the mitral annulus and then visually determine whether the UCA administration is optimal by assessing the homogeneity of LV cavity opacification from the apex to the mitral annular plane in the apical views. Gain and compression settings should be adjusted to reduce background signals coming from myocardium or blood. The sonographer should minimize shadowing or attenuation by lowering the infusion rate or reducing the size of the bolus injection and flush rate (Table 2). Attenuation observed with a bolus injection will resolve with time; thus, image acquisition should be delayed until the attenuation disappears. Once the attenuation is minimized, and apical swirling is not present, the sonographer can begin acquisition in the apical four-chamber, two-chamber, and long-axis views. In each view, if available, a high-MI "flash" impulse lasting three to five frames may be used to clear contrast from the myocardium. This improves endocardial visualization just after the impulse by creating excellent endocardial contrast and also permits analysis of contrast replenishment within the myocardium on subsequent frames. Because attenuation may result in difficult visualization of basal segments, purposely foreshortening the apical windows may improve delineation of these segments. From a time perspective, the skilled sonographer can complete an assessment of regional function and myocardial perfusion within 5 to 10 min when using very low MI "real-time" imaging modalities.

VI. SALINE CONTRAST OPTIMIZATION FOR TRANSTHORACIC AND TRANSESOPHAGEAL RIGHT-TO-LEFT SHUNT DETECTION

A saline contrast injection is indicated to rule out an intrapulmonary or intracardiac right-to-left shunt. A PFO has been associated with stroke, paradoxical emboli, decompression sickness, platypnea, and orthodeoxia.[29] Although the clinical significance of detecting a PFO by echocardiography is controversial, studies to evaluate these disease states routinely include saline contrast injections. The literature has clearly shown the advantage of transesophageal echocardiography (TEE) over transthoracic echocardiography (TTE) in detecting these shunts,[30] but screening procedures have still used TTE. Although color Doppler is primarily used to detect ventricular septal defects, saline contrast is still useful in this setting to assess for right-to-left shunting and to detect residual shunts after defect closure.[30] Bolus injection of sterile saline contrast macroscopic bubbles that do not normally cross the pulmonary circuit is the method of choice to screen for a PFO. It is recommended that the saline contrast be composed of ≥8 mL of bacteriostatic normal saline agitated with 0.5 mL of room air, agitated back and forth between two sterile syringes using a three-way stopcock just before IV bolus injection through a forearm or hand vein. Specific physiologic maneuvers and admixtures of saline with the patient's blood have been proposed to optimize the contrast produced in the right atrium[31] and detect any passage into the left

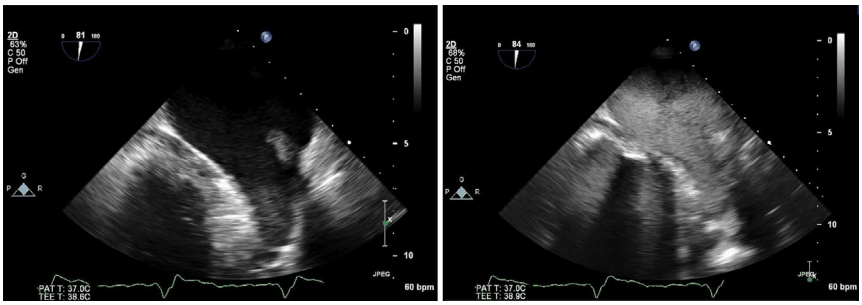

Figure 5 A transesophageal echocardiogram before (*left*) and after (*right*) an IV bolus injection of a transpulmonary contrast agent to confirm that the questionable mass in the left atrial appendage (LAA) was just spontaneous contrast. The IV microbubbles completely fill the LAA (*right*). (See Video 10; available at www.onlinejase.com).

atrium (Table 3). It is important that release of a Valsalva maneuver or coughing (to transiently increase right atrial pressure) occur when the saline contrast bolus arrives in the right atrium. It would be optimal for the sonographer to have ≥20-gauge cannula access in a good forearm or antecubital vein (preferably on the patient's right side if the patient is lying on the left side for imaging). Optimal visualization of the interatrial septum (via either a foreshortened apical window or subxiphoid window) and use of tissue-harmonic imaging to optimize bubble detection are key features to improving the sensitivity to shunt detection.

Both right- and left-arm saline contrast injections should be used whenever a persistent left-sided superior vena cava or unroofed coronary sinus is suspected. Although femoral venous injections improve flow directed to the septum, these are too invasive for routine sonographer use in detecting a PFO.[32] Sonographers should also be aware that typical intracardiac shunts (via the interatrial or interventricular septum) are usually seen within the first three beats of right atrial opacification, while pulmonary arteriovenous shunts are at least five beats after right atrial opacification. However, it is important to note that saline contrast may appear sooner with pulmonary arteriovenous shunts in high-output states, and saline contrast across a PFO may occur later than three beats if there is delayed coughing or Valsalva maneuvers. Also, false-negative saline contrast studies can occur if the interatrial septum is persistently bowed toward the right atrium during agitated saline injection, as a PFO can be held closed with the septum in this position. If there is still suspicion that a PFO exists after negative results, a repeat saline contrast injection should be performed using a blood-saline-air mixture or a more appropriately timed Valsalva or cough maneuver to ensure that the results are truly negative. Universal precautions should be adhered to with this technique to avoid bloodborne pathogen exposure. With TEE, direct visualization of the septum secundum and septum primum is recommended during saline contrast injection, to document the location and size of any right-to-left shunt. Image acquisition should be timed to begin just before the appearance of saline contrast in the right atrium and continue for at least 10 cardiac cycles after contrast appearance.

VII. FUTURE CONTRAST DEVELOPMENTS FOR THE SONOGRAPHER

This update for UCA use is designed to assist all sonographers in the optimal use of UCAs with currently available ultrasound scanner software. However, approval is being sought in the United States for other UCAs, such as SonoVue, which has been approved for several years in Europe. This agent will have unique features that may require updates, should it be approved. SonoVue is a lipid-encapsulated sulfur hexafluoride–containing microbubble that also is administered as an infusion or as small boluses during real-time very low MI imaging.[33]

Furthermore, three-dimensional imaging is being used more for valvular disease and quantification of LV and right ventricular ejection fractions. Real-time three-dimensional echocardiography has been used to improve regional wall motion analysis during resting and stress echocardiography.[34] Recent clinical studies have demonstrated a potential role for UCAs in improving LV regional wall motion and ejection fraction assessments.[35,36] However, contrast use for three-dimensional acquisitions will require optimization of settings similar to what has been used for two-dimensional transducers, with greater attention to minimizing LV apical swirling. To date, real-time very low MI software is not routinely available with three-dimensional scanners. The writing group recommends that this software be implemented in all three-dimensional packages to achieve optimal LVO and perfusion assessments in all 17 segments.

With regard to automated border detection algorithms, they are not currently designed for detecting a bright cavity border with contrast, but the writing group strongly recommends that manufacturers of automated border detection software redesign their algorithms for contrast media, as this may further improve the accuracy and applicability of this software.

Use of transpulmonary contrast agents during TEE has recently been described for better delineation of a left atrial appendage thrombus and differentiating between spontaneous contrast and thrombus (Figure 5). Normal results on TEE when using transpulmonary contrast to exclude a thrombus before cardioversion for atrial fibrillation have been associated with a lower risk for stroke or systemic embolization.[37] Modifications in TEE transducer design to include very low MI real-time sequences may further improve transpulmonary contrast use during TEE.

In the area of vascular imaging, contrast may also prove useful in improving carotid plaque visualization (especially soft plaque) and visualization of the vasa vasorum. It may also be useful for the detection of endoleaks after stent graft placement in abdominal aortic aneurysms.[38] In this area, as well as in other peripheral vascular applications, the writing group recommends the development of specific indications for when they should be used, as well as imaging protocols.

VIII. RECOMMENDED INITIATIVES

The writing group recommends that consideration be given to programs and initiatives that will help sonographers improve the use of contrast in critical care settings. The beneficial effects of contrast are

becoming increasingly recognized in critical care situations, in which the early use of contrast after hospital admission may improve mortality.[39] An example of this is demonstrated in Video 11; available at www.onlinejase.com, in which very low MI imaging with contrast detected an inferolateral wall motion abnormality that was not identified with conventional tissue-harmonic imaging. Note that this wall motion abnormality was not detectable even with good endocardial border resolution. The value of contrast in critical care settings extends to patients with advanced heart failure, in whom the use of contrast enhancement in LV assist devices may improve the detection of thrombi adherent to inflow or outflow cannulas, or pseudoaneurysms (Video 5; available at www.onlinejase.com).[40,41] The committee highly recommends that prospective studies be conducted to evaluate the value of contrast in critical settings.

Although many new applications are being developed, it is also evident that contrast media use for current applications is not being performed uniformly in different institutions, and overall use is inappropriately low. The writing group supports the following initiatives to ensure appropriate use:

1. Working with various organizations (e.g., the IAC, the International Contrast Ultrasound Society) to increase awareness of the value of contrast media in critical care settings, emergency departments, and during stress echocardiography.
2. Rebranding the term "contrast" or "ultrasound contrast agent" to "ultrasound enhancing agent."
3. Increasing the number of sonographers who are trained in starting IV lines and administering UCAs
4. Recommending that industry implement very low MI software for all two- and three-dimensional platforms. These should not be branded "real-time perfusion" software but "optimal enhancement" software.

The writing group encourages sites to consider the appropriate use of contrast in settings in which its use has been shown essential to improve early patient diagnosis and management. This would include intensive care units, emergency department evaluation of CP, and stress echocardiography. The writing group recommends an initiative to rebrand UCAs as ultrasound enhancement agents. The purpose of this would be to improve patient, sonographer, and physician understanding that we are not using ionizing radiation or nephrotoxic agents. The writing group strongly advises sonographers and physicians to work with hospital administrations to develop standard operating procedures that increase the availability of qualified personnel who can start IV lines and administer UEAs. Finally, very low MI software should be available on *all* current ultrasound equipment and should not be termed "real-time perfusion" but rather "optimal enhancement," because these pulse-sequence schemes reduce microbubble destruction and enhance the visualization of endocardial borders better than current low-MI harmonic software packages.

This document is designed to help sonographers overcome the technical and administrative barriers to contrast utilization. With further technological modifications and the adoption of ultrasound enhancement agents into clinical echocardiographic practice, we anticipate additional updates to these guidelines in the future.

NOTICE AND DISCLAIMER

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.echo.2014.05.011.

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APPENDIX

Best Practices for Contrast Administration

Facility: Oregon Health & Science University

Personnel – IV Start: Sonographer/registered nurse (RN)/fellow/physician

Personnel – Contrast Administration: Sonographer/RN/fellow/physician

Personnel – Agitated Saline Administration: Sonographer/RN/fellow/physician

Process for Order: Outpatients—order written on paper order and scanned into electronic medical record (EMR). Inpatients—order entered into EMR and cosigned by the attending echocardiographer.

Consent and/or Education: Education with respect to risks associated with reaction

Contrast Preparation and Injection:

Infusion

1. Withdraw 27 mL (for Optison) or 28.5 mL (for Definity) of 0.9% normal saline into a 35-mL syringe.
2. Using an Optispike, withdraw the contents of a vial of Optison (3 mL) or Definity (1.5 mL) into the saline syringe. Leave 0.5 mL of airspace within the syringe to help keep the microbubbles suspended. Gently rotate the syringe to mix the contrast agent in the syringe.
3. Attach microbore tubing to the syringe and flush through with the diluted contrast agent.
4. Insert the syringe into a syringe pump.
5. For most patients, an infusion rate of approximately 90 mL/h will provide good LVO/endocardial border delineation.
6. Adjust infusion rate to obtain adequate enhancement, while minimizing far-field attenuation.

Contrast Purpose/Indication: To optimize the assessment of LV function in patients with suboptimal acoustic windows or to provide an accurate and reproducible quantitative LV ejection fraction. Other benefits of contrast agents include delineation of intracavitary masses (e.g., thrombi, tumors), apical abnormalities (apical hypertrophic cardiomyopathy, noncompaction, aneurysm, or pseudoaneurysm), and enhancement of Doppler signals in the systemic circulation (pulmonary venous inflow, aortic flow signal).

Agitated Saline Supplies, Preparation and Injection:

Supplies

10-mL single-dose vial bacteriostatic 0.9% sodium chloride
Three-way stopcock
T extension
10-mL Luer-Lok (2) syringes
IV catheter
Tourniquet
Alcohol preparation pads
Tape
4 × 4 gauze
Band-Aid
Gloves

Preparation. Using two 10-mL syringes, fill one syringe with 10 mL bacteriostatic 0.9% sodium chloride and attach to the three-way stopcock, then attach the other 10-mL syringe with 1 mL air to the other side of the stopcock. Use the stopcock to block access to the venous and agitate saline and air vigorously between the two syringes, and when both the injector and the image are ready, open stopcock access to the venous system and inject agitated saline rapidly.

Facility: Medical University of South Carolina

Personnel – IV Start: Sonographer/RN/nurse practitioner (NP)/fellow/physician

Personnel – Contrast Administration: RN/NP/fellow/physician

Personnel – Agitated Saline Administration: Sonographer/RN/NP/fellow/physician

Process for Order: Cardiology fellow or attending cardiologist approves and provides order

Consent and/or Education: Outpatients sign consent. Inpatients are educated with respect to risks associated with reaction.

Contrast Preparation and Injection:

Supplies. Optison
(1) Bacteriostatic saline (sodium chloride)
(1) 3-mL syringe
(1) 3- or 5-mL syringe

Preparation. Rotate Optison vial between the palms of the hands for about 20 sec to shake up the microspheres.

Optison must then be vented with a sterile vent spike or a sterile 18-gauge needle.

Withdraw 3 mL into 3-mL syringe.

Always flush IV line with saline before injecting Optison to ensure the IV line is working.

Inject 1 mL Optison *slowly* over 10 sec.

Wait for complete LVO and begin capturing images in the following order: four-chamber, two-chamber, three-chamber, parasternal long-axis and parasternal short-axis of left ventricle, and parasternal short-axis of apex. Make sure to label the images.

Inject more contrast as needed and repeat the steps above.

Optison lasts about 7 to 8 min, depending on the patient's body surface area.

When the test is complete, flush the IV line with 3 or 5 mL saline.

Measure blood pressure and perform visual assessment of patient prior to discharge if outpatient.

Contrast Purpose/Indication:

1. When at least two LV wall segments cannot be visualized
2. To determine whether LV thrombus formation exists
3. To enhance spectral Doppler

Facility: Houston Methodist Hospital

Personnel – IV Start: Sonographer/RN/NP/fellow/physician

Personnel – Contrast Administration: Sonographer/RN/NP/fellow/physician

Personnel – Agitated Saline Administration: Sonographer/RN/NP/fellow/physician

Process for Order: Built into order entry—Complete echocardiography with contrast and/or three-dimensional imaging if needed

Consent and/or Education: Education with respect to risks associated with reaction

Contrast Preparation and Injection:

Pharmaceutical contrast must be vented with a sterile vent spike or a sterile 18-gauge needle. Do not inject air into the vial.

Dosing and Administration. *Bolus: We do not bolus in this laboratory*

1. Clinical experience has shown that an initial dose of 0.5 mL of diluted contrast as described above and followed by consecutive doses as needed is most effective.
2. The pharmaceutical contrast injection is then followed by a 1- to 2-mL flush of normal saline, pushed slowly (only enough to get the product circulating into the vein).

Diluted Infusion:

1. Add 2 mL Definity or 3 mL Optison to 50 mL 0.9% sodium chloride that is preservative free.
2. The rate of infusion should be initiated at 4.0 mL/min and then titrated appropriately.
3. Always flush the IV site when finished with a contrast examination.

Definity maximum total dose is two vials or 4.0 mL.
Optison maximum total dose is 8.7 mL.

Contrast Purpose/Indication:

1. Contrast is indicated for use in patients with suboptimal echocardiograms for LVO to improve the delineation of the LV endocardial borders at rest or with exercise and/or pharmacologic stress.
2. Ultrasound contrast may be used to optimize Doppler signals in stenotic valves when there is a suboptimal Doppler signal. If used, turn the Doppler gain setting down to 20% or lower.
3. The risk benefit and use of either contrast media for patients with contraindications will be assessed by the attending cardiologist, cardiology fellow, or ordering physician.

Agitated Saline Supplies, Preparation and Injection:

1. All patients receive a thorough explanation of the test before it is performed.
2. IV preparation supplies: (1) 10-mL single-dose vial of bacteriostatic 0.9% sodium chloride, (1) three-way stopcock, (1) T extension, (2) 10-mL Luer-Lok syringes, (1) IV catheter, tourniquet, alcohol preparation pads, tape, 4 × 4 gauze, Band-Aid, and gloves.
3. IV insertion and agitated saline administration:
   a. The nurse/sonographer will insert a temporary saline lock.
   b. Draw up 10 mL sodium chloride solution in the 10-mL syringe. Flush T piece and stopcock with sterile normal saline before connecting to the angiocath.
   c. The T-piece extension and stopcock are attached to the angiocath after insertion.
   d. Connect the two 10-mL syringes to the stopcock, one with and one without saline.
   e. Agitate between the two 10-mL syringes by turning the stopcock arrow to permit agitation.
   f. When the saline solution appears fully agitated (opaque), the nurse, registered sonographer, or fellow will inject. If needed, 1 mL air or blood can be added for enhancement.
   g. Several injections may be made in different views selected by the sonographer.
   h. Discontinue IV line when contrast study is completed.

Facility: Mayo Clinic, Rochester, Minnesota

Personnel – IV Start: RN
Personnel – Contrast Administration: RN
Personnel – Agitated Saline Administration: RN
Process for Order: Electronic order for echocardiography; on arrival in echocardiography laboratory, a standing order policy exists to empower the sonographer to give contrast if more than two segments are not visualized in any one view, provided the patient has no allergy to the product or has a known or suspected hemodynamically significant right-to-left or bidirectional cardiac shunt (excluding PFO) or, if Optison, the patient has had a transfusion reaction to blood, blood products, or albumin. If any exceptions are present, the supervising echocardiography consultant is notified to review and make the decision to give contrast.
Consent and/or Education: An RN performs patient education assessment; instructs the patient on the risks, benefits, and possible side effects; and obtains verbal consent.

Contrast Preparation and Injection:

Perflutren Lipid Microsphere (Definity).

1. Activate perflutren lipid microsphere by shaking the vial for 45 sec using a Vialmix.
2. Draw up the contents of the vial into a 10-mL syringe with 8.5-mL of 0.9% sodium chloride for a total of 10 mL.
3. Administer 0.5-mL IV push of the diluted solution, then flush over 10 sec with 3 mL 0.9% sodium chloride to clear the tubing.
4. Monitor the visualization of images.
5. If images are still not optimal, administer an additional 0.5-mL IV push of the diluted solution followed by a 3-mL flush of 0.9% sodium chloride to clear the tubing. Repeat as needed until images are optimal or a total of 10-mL of diluted solution has been administered.

Perflutren Protein–Type A Microspheres (Optison).

1. Administer 0.3-mL IV push over 10 sec, followed by 3 mL of 0.9% sodium chloride.
2. Monitor the visualization of images.
3. If images are still not optimal, repeat step 1 until images can be obtained (not to exceed 5 mL in any 10-min period, up to a maximum dose of 8 mL per study).

Contrast Purpose/Indication:
INCLUSION CRITERIA (standing order policy):

- To enhance endocardial border definition
- To assess for cardiac mass or thrombus
- To assess myocardial perfusion
- To enhance Doppler signals

If at least one of above is present, proceed to contrast administration section. Otherwise, protocol does not apply, and discussion with the supervising physician is needed.

Agitated Saline Supplies, Preparation and Injection:

1. For TTE or TEE: Place a peripheral IV line as needed following Mayo nursing procedural guidelines. Extension tubing and a three-way stopcock should be attached to the IV catheter hub and secured.
2. For use of agitated saline during pericardiocentesis to confirm catheter position: a three-way stopcock should be attached to the polytef sheath and secured.
3. Prepare two syringes; one should contain 5 mL saline, the other should be empty.
4. Connect the syringes to the three-way stopcock. Aerate the saline by rapid injection back and forth between the two syringes.
5. Rapidly inject the agitated saline into the IV line (for TTE and TEE) or polytef sheath (for pericardiocentesis) and observe the contrast effect with two-dimensional echocardiography.
6. The apical four-chamber view should be obtained at rest and then again with a Valsalva maneuver. Other views may be considered if indicated.
7. Repeat procedure throughout study as needed.

Facility: University of Nebraska Medical Center—Definity

Personnel – IV Start: RN (echocardiography nurse) or RN (lead on floor) will start IV and administer the contrast
Personnel – Contrast Administration: RN or cardiology fellow will administer contrast via continuous infusion. Sonographer or physician will acquire images.
Personnel – Agitated Saline Administration: RN/sonographer/fellow/physician
Process for Order: Built into order entry (EMR)—Complete echocardiographic study with contrast if needed.
Consent and/or Education: Education with respect to risks associated with reaction

Contrast Preparation and Injection:

Supplies.

1. Definity
2. 20-gauge or larger IV cannula
3. Y-site connector
4. 10-mL saline flush
5. Tegaderm
6. 30-mL syringe
7. 0.9% sodium chloride injection USP
8. Dispensing pin with SAFSITE valve
9. Four-way stopcock
10. 1-mL syringe
11. Lever Lock cannula
12. Blunt plastic cannula

Continuous Infusion with Definity:

1. Activate Definity by agitating vial for 45 sec in a Vialmix.
2. Use a 20-gauge or larger IV cannula.
3. Attach the IV cannula to a Y connector. This setup will allow the use of Definity and a stress agent if needed. The IV line should be placed in a large vein in the right arm. (Left-arm IV placement can sometimes inhibit the flow of Definity into the heart).
4. Inpatient IV sites must be checked for redness or swelling. The existing IV site should have good blood return. Blood return can be checked by inserting a syringe of normal saline into the IV site and pulling back slightly.
5. With the use of the dispensing pin with SAFSITE valve, prepare two syringes of 29 mL 0.9% normal saline and attach a four-way stopcock to each. Attach a Lever Lock cannula to the tip of each syringe.
6. Definity must be refrigerated between 2°C and 8°C. Definity should be allowed to come to room temperature before activation. Never inject air into the vial. Using a blunt plastic cannula slowly draw up 0.8 mL of contrast into a 1-mL syringe. Unscrew the red cap from the four-way stopcock and attach the syringe of contrast to the four-way stopcock. The syringe of normal saline should be attached to another port of the stopcock. Inject the Definity into the normal saline syringe. Screw on the red cap and mix the solution gently in figure-of-eight hand rotations. Attach the stopcock to the Y connector at the patient's IV site.
7. The contrast should not be mixed into the saline until just before infusion.
8. The nurse or designated personnel will administer the Definity as a continuous infusion.
9. Inject at a rate of 1 mL every 15 sec, or titrate to achieve the best quality images.
10. Activated Definity appears as a milky white suspension and may be used immediately after activation. If the product is not used within 5 min of activation, the Definity should be resuspended by 10 sec of hand agitation by inverting the vial before the product is withdrawn in a syringe.

Contrast Purpose/Indication:

1. Suboptimal images defined as the inability to detect two or more contiguous segments in any three of the apical windows.
2. Quantification of chamber dimensions, volumes, ejection fraction, assessment of regional wall motion, and intracardiac masses or thrombi.
3. To enhance spectral Doppler

Agitated Saline Supplies, Preparation, and Injection:

1. Obtain a physician's order.
2. Start an IV line, or assess the existing IV line for patency.
3. Mix 9 mL 0.9 normal saline with 1 mL blood drawn back or air in a 10-mL syringe. Attach a stopcock to the syringe. Attach a second empty syringe to the stopcock.
4. Attach the stopcock to the IV line. Quickly mix the saline back and forth between the two syringes until it is bubbly.
5. Let the sonographer know before injecting. Turn the stopcock off to one syringe and inject the agitated saline into the IV line as quickly as possible.
6. Raise the patient's arm to facilitate the saline solution flowing rapidly into the right heart.
7. Document as required.

Facility: University of Nebraska Medical Center—Optison

Personnel – IV Start: RN (echocardiography nurse) or RN (lead on floor) will start IV and administer the contrast.

Personnel – Contrast Administration: RN or cardiology fellow will administer contrast via continuous infusion. Sonographer or physician will acquire images.

Personnel – Agitated Saline Administration: RN/sonographer/fellow/physician

Process for Order: Built into order entry (EMR)—Complete echocardiographic study with contrast if needed.

Consent and/or Education: Education with respect to risks associated with reaction

Contrast Preparation and Injection:

Supplies.

1. Optison
2. 20-gauge or larger IV cannula
3. Y site connector
4. 10-mL saline flush
5. Tegaderm
6. 30-mL syringe
7. 0.9% sodium chloride injection USP
8. Dispensing pin with SAFSITE valve
9. Four-way stopcock
10. 3-mL syringe
11. Lever Lock cannula
12. Optispike

Continuous Infusion with Optison:

1. Use 22-gauge or larger IV cannula.
2. Attach the IV cannula to a Y connector. This set up will allow the use of Optison and a stress agent if needed. The IV line should be placed in a large vein in the right arm. (Left-arm IV placement can sometimes inhibit the flow of Optison into the heart).
3. Inpatient IV sites must be checked for redness or swelling. The existing IV site should have good blood return. Blood return can be checked by inserting a syringe of normal saline into the IV site and pulling back slightly.
4. Optison must be refrigerated between 2°C and 8°C. Resuspend by inverting and gently rotating the vial until the mixture in the vial appears milky and uniform. Vent the vial with an Optispike. Never inject air into the vial. Slowly draw up 3.0 mL Optison. Attach the syringe to a four-way stopcock. A syringe of 0.9% normal saline (20 mL) should be attached to another port of the stopcock. Infuse 1.5 mL Optison into the 0.9% normal saline and mix until suspended. Attach the stopcock to the Y connector at the patient's IV site.
5. Optison will stay suspended for approximately 1 min. To ensure the best results, the syringe containing Optison should be inverted or gently rotated between patient injections. Check before injecting to make sure that Optison's appearance is milky and uniform.
6. The nurse or designated personnel will administer the Optison as a continuous infusion.
7. Slowly inject the Optison suspension into the IV line. The injection should be visible in the right side of the heart within a few seconds. The total dose of Optison should not exceed 5 mL in 10 min or 8.7 mL in any one patient study.

Contrast Purpose/Indication:

1. Suboptimal images, defined as the inability to detect two or more contiguous segments in any three of the apical windows.
2. Quantification of chamber dimensions, volumes, ejection fraction, assessment of regional wall motion, and intracardiac masses or thrombi.
3. To enhance spectral Doppler.