Clinical Applications of Ultrasonic Enhancing Agents in Echocardiography: 2018 American Society of Echocardiography Guidelines Update

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Abbreviations

2D = Two-dimensional
3D = Three-dimensional
ASE = American Society of Echocardiography
CAD = Coronary artery disease
CHD = Congenital heart disease
CMRI = Cardiac magnetic resonance imaging
COR = Class of recommendation
CPT = Current Procedural Terminology
CT = Computed tomography
DSE = Dobutamine stress echocardiography
DUS = Diagnostic ultrasound
ECG = Electrocardiography
ED = Emergency department
FDA = US Food and Drug Administration
ICU = Intensive care unit
IV = Intravenous
LOE = Level of evidence
LV = Left ventricular
LVEF = Left ventricular ejection fraction
LVO = Left ventricular opacification
MBV = Microvascular blood volume
MCE = Myocardial contrast echocardiography
MI = Mechanical index
MP = Myocardial perfusion
OR = Odds ratio
PAD = Peripheral arterial disease
RCT = Randomized controlled trial
RTMCE = Real-time myocardial contrast echocardiography
RWM = Regional wall motion
SPECT = Single-photon emission computed tomography
STEMI = ST-segment elevation myocardial infarction
TEE = Transesophageal echocardiography
TTE = Transthoracic echocardiography
UEA = Ultrasound enhancing agent
UTMD = Ultrasound-targeted microbubble destruction
VLMI = Very low mechanical index

I. INTRODUCTION

The use of ultrasound enhancing agents (UEAs) has become an integral component of echocardiography practice. Since the 2008 American Society of Echocardiography (ASE) consensus statement on clinical applications of ultrasound contrast agents,[1] there have been several important developments that require the document be revised into a guidelines paper.

1. The term *ultrasound contrast agents*, describing a class of products comprising microbubbles to enhance ultrasound signals,[2-5] was replaced with the less conflicting term *ultrasound enhancing agent*. Although the Writing Group understands the need for this terminology in helping patients and referring physicians distinguish these substances from iodinated contrast agents or gadolinium chelates, it was considered equally acceptable to refer to these agents as contrast agents and the imaging techniques as contrast echocardiography or myocardial contrast echocardiography (MCE).
2. The Intersocietal Accreditation Commission has required that policies be in place for UEA use (section 1.6.2.4B, updated June 1, 2017) in specific clinical settings in which UEAs are required.[6]
3. The safety of UEAs has been documented in several different clinical scenarios (stress echocardiography, pulmonary hypertension, intracardiac shunting) as well as in emergency department (ED), critical care, and pediatric settings.[5] Propensity-matched studies have not only documented safety but also demonstrated the potential value and importance of early UEA use in improving patient outcomes (Table 1). These large single- and multicenter studies have led to changes in the US Food and Drug Administration (FDA) boxed warnings regarding UEA use in pulmonary hypertension, critical care settings, and more recently, known or suspected right-to-left shunts.
4. Numerous clinical trials have demonstrated the safety and efficacy of UEAs in new stress echocardiography settings (dipyridamole, adenosine, regadenoson, bicycle, and treadmill), as well as in different resting conditions in which regional wall motion (RWM) and perfusion information provide significant incremental value in predicting patient outcomes (Table 2).
5. The use of myocardial perfusion (MP) imaging with UEAs has increased, specifically in the setting of stress echocardiography, chest pain evaluation in the ED, and in the evaluation of intracardiac masses.[25,34,35] The American Medical Association Current Procedural Terminology (CPT) Panel approved a category III ("emerging technology") CPT code (+0439T) for "myocardial contrast perfusion echocardiography; at rest or with stress, for assessment of myocardial ischemia or viability" (effective July 1, 2016) for the use of perfusion imaging as an add-on to the following base CPT codes: 93306, 93307, 93308, 93350, and 93351. Although this category III code is not reimbursed by the Centers for Medicare and Medicaid Services in the United States, approval of this code acknowledges the significant incremental value of MP with UEAs in several clinical settings.

Table 1 Large studies (>1,000 patients) published since 2008 that evaluated UEA safety

Study	Design	UEA	Total patients	UEA patients	Control patients	Inpatient/outpatient	Rest/stress	Outcomes
Aggeli *et al.* (2008)[7]	Prospective	Sonovue	5,250	5,250	NA	NR	Stress	No deaths or myocardial infarctions
Gabriel *et al.* (2008)[8]	Retrospective	Definity or Optison*	9,798	4,786	5,012	95% Outpatients	Stress	No increased rate of SAEs or mortality at 24 h in UEA patients
Herzog *et al.* (2008)[9]	Retrospective	Definity or Optison	16,025	16,025	NA	Both	Both	No short-term mortality; SAEs in 0.031%
Kusnetzky *et al.* (2008)[10]	Retrospective	Definity	18,671	6,196	12,475	Inpatients	Rest	No increased mortality in UEA patients
Main *et al.* (2008)[11]	Retrospective	Definity	4,300,966	58,254	4,242,712	Inpatients	Rest	No increased mortality in UEA patients
Shaikh *et al.* (2008)[12]	Retrospective	Definity or Optison	5,069	2,914	2,155	Both	Stress	No increased risk for SAEs in UEA patients
Wei *et al.* (2008)[13]	Retrospective	Definity or Optison	78,383	78,383	NA	Both	Both	Severe allergic reactions in 0.01% and anaphylactoid reactions in 0.006%
Abdelmoneim *et al.* (2009)[14]	Retrospective	Definity or Optison	26,774	10,792	15,982	Both	Stress	No increased short- or long-term mortality in UEA patients
Anantharam *et al.* (2009)[15]	Retrospective	Definity or Lumason†	3,704	1,150	2,554	Both	Stress	No increased SAEs in UEA patients
Dolan *et al.* (2009)[16]	Retrospective	Definity or Optison	66,220	42,408	23,812	NR	Both	No increased mortality in UEA patients
Abdelmoneim *et al.* (2010)[17]	Retrospective	Definity or Optison	16,434	6,164	10,270	Both	Stress	No increased risk for myocardial infarction or mortality in UEA patients with pulmonary hypertension
Exuzides *et al.* (2010)[18]	Retrospective	Optison	14,500	2,900	11,600	Inpatients	Rest	No increased mortality in UEA patients
Goldberg *et al.* (2012)[19]	Retrospective	Definity	96,705	2,518	94,187	Both	Both	No increased mortality in UEA patients
Weiss *et al.* (2012)[20]	Prospective	Definity	1,053	1,053	NA	NR	Both	No deaths or SAEs
Wever-Pinzon *et al.* (2012)[21]	Retrospective	Definity	1,513	1,513	NA	Inpatients	Both	No deaths or SAE attributed to UEA in pulmonary hypertension patients
Platts *et al.* (2013)[22]	Retrospective	Definity	5,956	5,956	NA	Both	Both	No increased mortality in UEA patients
Main *et al.* (2014)[23]	Retrospective	Definity	32,434	16,217	16,217	Inpatients	Rest	Lower mortality in UEA patients
Wei *et al.* (2014)[24]	Prospective	Optison	1,039	1,039	NA	Outpatients	Both	No deaths or SAEs

NA, Not applicable; *NR*, not reported; *SAE*, serious adverse event.
Modified with permission from Muskula *et al.*[25]
*Definity is marketed as Luminity in Europe.
†Lumason is marketed as SonoVue in Europe.

Table 2 Smaller studies (<1,000 patients) published since 2009 that evaluated UEA safety

Study	Design	UEA	Total patients	UEA patients	Control patients	Inpatient/outpatient	Modality	Outcomes
Kurt *et al.* (2009)[26]	Prospective	Definity	632	632	NA	545 inpatient, 87 outpatient	Rest	1 serious AE, 5 minor AEs (back pain)*
Senior *et al.* (2013)[27]	Prospective	Sonovue	630	628	NA		Stress	1 serious AE, 16 minor AEs, 2.5% (nausea, headache)†
Main *et al.* (2013)[28]	Prospective	Optison	33	30	NA	Outpatient	Rest (PASP > 35 mm Hg)	No serious AEs
Wei *et al.* (2012)[29]	Prospective	Definity	32	32	16 with PASP < 35 mm Hg	Outpatient	Rest (16 with PASP > 35 mm Hg)	No serious AEs, 1 mild AE (back pain, headache)
Kutty *et al.* (2016)[30]	Retrospective	Definity	113	113	140	Outpatient	Rest and stress	13 minor AEs (<1 min in duration, no treatment)
Fine *et al.* (2014)[31]	Retrospective	Definity, Optison	251	10	NA	Inpatient	LVAD patients	No complications related to UEA, no AEs, no change in device parameters
Bennett *et al.* (2016)[32]	Retrospective	Perflutren, Definity, Optison	1,996	4	NA	Inpatient	ECMO patients	No complications related to UEA, no AEs, no change in device parameters
Kalra *et al.* (2014)[33]	Retrospective	Definity, Optison	39,020 UEA patients	418 with right-to-left shunts‡	NA	NA	Rest	No primary AEs, 1 minor AE (back pain) in the shunt group

AE, Adverse event; *ECMO*, extracorporeal membrane oxygenation; *LVAD*, LV assist device.

*Death after 5 hours of UEA administration; patient experienced a large anterior wall myocardial infarction after knee replacement with hypotension, recurrent ventricular tachycardia within the 24 hours before echocardiography.

†A 69-year-old woman with suspected myocarditis developed hypersensitivity-like symptoms and asystole for 30 sec (symptom-free recovery within 57 min).

‡Left-to-right shunts excluded.

Table 3 The three commercially available UEAs

Name	Manufacturer/vial contents	Mean diameter	Shell	Gas	Contraindications
Lumason (sulfur hexafluoride lipid-type A microspheres)	Bracco Diagnostics, 5 mL	1.5–2.5 μm (maximum 20 μm, 99% $\leq$10 μm)	Phospholipid	Sulfur Hexafluoride	Allergy to sulfur hexafluoride
Definity (perflutren lipid microsphere)	Lantheus Medical Imaging, 1.5 mL	1.1–3.3 μm (maximum 20 μm, 98% <10 μm)	Phospholipid	Perflutren	Allergy to perflutren
Optison (perflutren protein type-A microspheres)	GE Healthcare, 3.0 mL	3.0–4.5 μm (maximum 32 μm, 95% <10 μm)	Human albumin	Perflutren	Allergy to perflutren/ blood products

Table 4 Location and description of VLMI imaging software on commercially available echocardiographic scanners

Manufacturer	Platform and portability*	Location and name of enhanced imaging software on front end	High-MI "flash" impulse location on front end	Specific pulse sequence scheme used (dominant nonlinear activity detected)	Frequency/MI recommended for VLMI imaging
Philips	iE33 Not portable	Contrast key On/off LVO and low-MI choices	Touch screen/ flash label	Amplitude modulation and pulse inversion (fundamental and harmonic)	<2.0 MHz/MI < 0.2 (GEN or PEN setting)
Philips	Epiq Not portable	Contrast key On/off Low-MI and LVO choices	Touch screen/ flash label	Amplitude modulation and pulse inversion (fundamental and harmonic)	<2.0 MHz/MI < 0.2 (GEN or PEN setting)
Philips	CX50 Portable	Contrast key On/off LVO choice	Control panel	Amplitude modulation (harmonic)	<2.0 MHz/MI < 0.3
GE	Vivid E95 Not portable	Advanced contrast option	Touch screen/ flash label	Pulse inversion 1.5/3.0 and 1.6/3.2 MHz and 1.7/ 3.4 MHz (harmonic) Amplitude modulation 2.1 and 2.4 MHz (fundamental and harmonic)	1.5–1.7 MHz/MI < 0.2 2.1–2.4 MHz/MI < 0.2
Siemens	SC2000 Not portable		Not available; need to use "color Doppler" knob	Pulse inversion and alternating polarity/amplitude (fundamental and harmonic)	2.0 MHz/MI < 0.2
Toshiba	Aplio i900 Not portable	Touch screen/ CHI label	Control panel	Pulse subtraction (amplitude modulation; harmonic)	h3.5/MI < 0.2 (PEN setting)
Toshiba	Aplio 500 Not portable	Touch screen/ low label	Touch screen/ flash label	Pulse subtraction (amplitude modulation; harmonic)	h2.8–h3.6/MI < 0.2
Esaote	MyLabEight Not portable	Contrast key On/off LVO choice	Touch screen/ flash label	Phase cancellation	PEN frequency/MI < 0.2
Esaote	MyLabSeven Not portable	Contrast key On/off LVO choice	Touch screen/ flash label	Phase cancellation	1.5 MHz/MI < 0.2
Esaote	MyLabAlpha Portable	Contrast key On/off LVO choice	Touch screen/ flash label	Contrast tuned imaging	1.5 MHz/MI < 0.2

CHI, Contrast Harmonic Imaging; *GEN*, general harmonic frequency setting; *LVO*, left ventricular opacification; *MI*, mechanical index; *PEN*, lower fundamental frequency for harmonic imaging; *VLMI*, very low mechanical index (<0.2).
*Portable: defined as does not require wheels.

6. A critical mass of data have been published that demonstrates the beneficial effect of UEAs on early outcomes in critically ill patients and the cost-effectiveness of UEAs in patients with suboptimal windows in a wide variety of clinical settings.[5,25]

7. The FDA in the United States has approved new UEAs (Table 3). New agents have been approved in other North American and South American countries. Ultrasound manufacturers have also revised their left ventricular opacification (LVO) and low–mechanical index (MI) settings for optimal

enhancement.[36] Specific instrumentation guidelines are now provided to optimize left ventricular (LV) RWM and perfusion analysis (Table 4).

In recognition of the large volume of patients enrolled in prospective randomized studies, meta-analyses, registry data, and multicenter comparative effectiveness studies during rest and stress imaging, the Writing Group advises a class of recommendation (COR) and level of evidence (LOE) on diagnostic strategies using UEAs. The recommendations made are according to the updated 2015 American College of Cardiology/American Heart Association clinical practice guidelines[37] as follows:

COR

Class I (strong): Benefits are much greater than risks. The procedure should be performed.

Class IIa (moderate): Benefits are greater than risks, and the procedure can be useful if performed.

Class IIb (weak): Benefits are slightly greater than risks, and the procedure might be reasonable to perform.

Class III: The procedures offers no benefit or is harmful if performed.

LOE

Level A: High-quality evidence from more than one randomized controlled trial (RCT), a meta-analysis of high-quality RCTs, or one or more RCTs corroborated by high-quality registry data

Level B-R: Moderate-quality evidence from one or more RCTs or a meta-analysis of moderate-quality RCTs

Level B-NR: Moderate-quality evidence from one or more well-designed nonrandomized trials, observational studies, or registry studies or meta-analysis of such studies

Level C-LD: Randomized or nonrandomized observational or registry studies with limitations in design or execution or a meta-analysis of such studies

Level C-EO: Consensus based on clinical experience

This update focuses on the new data that have been published and how these data, when combined with the 2008 consensus statement and 2014 ASE contrast sonography guidelines,[1,38] have led to specific recommendations for UEA use in different clinical settings.

Key Points Regarding Current FDA Labeling of UEA Use

1. The only FDA-approved use for UEAs in cardiovascular disease is for LVO. However, given significant scientific literature support, other off-label uses of UEAs (such as MP, pediatric and vascular applications, and use during stress echocardiography) are recommended in the present document according to the 2015 clinical practice guidelines.[37]
   The approved indications for use of ultrasound enhancing agents are governed by each country and societal endorsement of this document does not imply otherwise.

II. COMPARING UEAs

Unlike red blood cells, which are poor scatterers of ultrasound, the microbubbles that compose UEAs are compressible and are of different density. This unique physical characteristic of microbubbles is important in understanding the behavior microbubbles exhibit when exposed to ultrasound energy. Currently there are three commercially available UEAs worldwide for cardiac imaging: Optison, Definity (Luminity in Europe), and Lumason (SonoVue outside the United States). Optison is available only in the United States and Europe, whereas Definity is marketed in the United States, Canada, Europe, Australia, and parts of Asia. Lumason is approved throughout North America, New Zealand, Europe, Brazil, and Asia.[5] The range of bubble sizes permits passage through the pulmonary circulation (1.1–4.5 μm in diameter). All contain a high–molecular weight gas that improves their persistence because of reduced solubility and diffusivity. Both Optison and Definity contain perflutren (octofluoropropane) gas, with the main difference being the flexible shell composition. The Optison shell is made up of human serum albumin, whereas Definity uses a phospholipid shell. Lumason consists of a sulfur hexafluoride gas core with a phospholipid shell (Table 3). The specific fatty acid chain length and charge, as well as the composition and length of the polyethylene glycol spacer, differ between Lumason and Definity.[3,4] Optison and Definity require refrigeration before use, whereas Lumason is stored as a dry powder without refrigeration. Preparation requirements for each of the agents differ: Definity requires activation with a mechanical agitator, Optison requires a resuspension of the bubbles by hand, and Lumason requires hand agitation.

Although Optison and Definity have been given as 10% and 3% to 5% diluted infusions in normal saline (Appendix),[38] Lumason has been primarily used in the United States as small 0.5-mL bolus injections followed by slow 5- to 10-mL saline flushes to avoid LV cavity shadowing. Because the Lumason vial contains 5 mL, these bolus injections can be repeated as needed to maintain homogenous cavity opacification.

There are other less widely available or developing UEAs. Sonazoid is a microbubble with a perfluorobutane gas core in a phosphatidylserine shell that received regulatory approval in 2007 for imaging of liver and breast tumors in Japan and South Korea. In 2014, it was approved for focal liver lesion imaging in Norway.[4]

Intravenous (IV) UEAs are currently approved in the United States by the FDA to enhance LVO in adults, although Lumason has also been approved for pediatric use and for liver imaging. Although not specifically approved for stress testing, UEAs have been shown to improve the detection of RWM abnormalities at rest and during stress testing.[38] All three approved UEAs have been shown to have excellent safety profiles.[34]

Key Points Regarding Currently Available Commercial UEAs

1. All currently approved commercial UEAs contain a high–molecular weight gas encapsulated in a flexible shell.
2. All are able to traverse pulmonary and systemic capillary beds, with a size range of 1.1 to 4.5 μm.
3. UEA persistence in the circulation is determined by microbubble size, gas composition (diffusivity and solubility), pharmacokinetics, and shell properties.
4. Three UEAs (Optison, Definity, and Lumason) are approved for use by the FDA for the indication of LVO; all other applications in cardiovascular disease are off-label uses. Lumason also has approval for adult and pediatric liver imaging, as well as evaluation for vesicoureteral reflux.

III. RECOMMENDATIONS FOR IMAGING OF UEAs

The signals obtained from UEAs are dependent on the MI of the transmitted ultrasound. The MI is directly related to the peak negative pressure and inversely related to the square root of the transmitted frequency. At a very low MI (VLMI) of <0.2, microbubbles begin to oscillate in an asymmetric manner, as the expansion phase is larger than the compression phase, generating an acoustic signal that is nonlinear in nature. A further increase in amplitude of the transmit wave may cause discontinuities in the microbubble shell as the oscillations become more exaggerated, effectively releasing the free gas to dissolve into the circulation. Additionally, gas can be driven out during compression of the microbubble, known as acoustically driven diffusion.

The nonlinear acoustic signal distinction is essential to allow effective differentiation of surrounding tissue signal from microbubble signal.[25,35]

As per the 2014 ASE contrast sonography guidelines,[38] VLMI represents multipulse cancelation sequences that are most effective at MI values <0.2, low MI represents harmonic imaging techniques that are used at MI values <0.3, intermediate MI represents harmonic imaging techniques used at MIs of 0.3 to 0.5, and high MI is any MI that exceeds 0.5. Real-time VLMI techniques are available on nearly all commercially available ultrasound imaging systems. These pulse sequence schemes permit the enhanced detection of microbubbles within the LV cavity and myocardium and thus permit improved RWM and perfusion analysis. The pulse sequence diagrams of available multipulse VLMI imaging techniques were published in Table 1 and Figure 1 of the 2014 ASE contrast sonography guidelines.[38] Pulse inversion (or phase inversion) is a tissue cancelation technique that delivers ultrasound pulses of alternating polarity (phase). Although pulse inversion provides excellent suppression of surrounding noncardiac tissue and results in high resolution by receiving only even-order harmonics, there is significant ultrasound signal attenuation, especially in basal myocardial segments of apical views in part because of filtering at higher frequencies. Power modulation (or amplitude modulation) detects fundamental and/or harmonic nonlinear activity almost exclusively from microbubbles when used at an MI < 0.2. This technique is also a multipulse cancelation technique, which varies the power, or amplitude, of each pulse, rather than the polarity. For example, at an MI of 0.05, both microbubbles and tissue respond in a linear fashion to the ultrasound pulse, whereas at twice this power (0.1), there is still a linear response from tissue but a nonlinear response from microbubbles. The linear responses from the two different pulses (the twice-amplified 0.05-MI response and the 0.1-MI response) can be subtracted from each other, thereby displaying only nonlinear behavior from the microbubbles. Although an increase in contrast enhancement is produced, this sequence scheme theoretically has reduced resolution and image quality compared with pulse or phase inversion imaging (which detects only higher frequency harmonic responses). Manufacturers have also combined these multipulse techniques by using both interpulse phase and amplitude modulation, which although more complex has the purpose of further enhancing nonlinear activity from microbubbles at a VLMI and canceling out the linear responses from surrounding tissue. The advantage of the VLMI imaging techniques, compared with B-mode low-MI harmonic imaging, is that there is better tissue cancelation, greater signal-to-noise ratio (sensitivity for detecting agent), and less microbubble destruction because of the lower MI required.[25] The overall clinical effect of VLMI imaging techniques is to provide high spatial and reasonable temporal resolution that permits the simultaneous assessment of MP and wall motion, which is especially important in detecting coronary artery disease (CAD; Videos 1 and 2; available at www.onlinejase.com). Because they detect the nonlinear activity at the fundamental frequency, power modulation and interpulse phase and amplitude modulation pulse sequence schemes have less attenuation and better microbubble contrast signal, resulting in improved apical and basal segment visualization (Videos 3 and 4; available at www.onlinejase.com). Specific instructions on optimizing image quality are given in Table 2 of the 2014 sonographer update.[38]

Continuous intermediate (MIs of 0.3 of 0.5) or high-MI imaging should be avoided because it causes destruction of microbubbles and creates swirling artifacts. However, brief (five to 15 frames) high-MI impulses (MIs of 0.8 to 1.2), which have been termed "flash impulses," can be used during VLMI imaging to clear contrast from the myocardium and enhance the delineation of endocardial borders. As discussed in detail later, the rate of myocardial contrast replenishment following the high-MI flash impulse has been used in combination with the plateau myocardial contrast intensity to assess MP.[35,36]

As outlined in the 2008 ASE consensus statement[1] and 2014 ASE guidelines for sonographers,[38] Doppler enhancement of left- and right-sided Doppler signals can be achieved with UEAs, and this has been useful for both adult and pediatric applications. Although there are no new clinical studies formally evaluating this, the guidelines committee continues to strongly recommend their use for enhancement of tricuspid regurgitant peak velocity jet detection (for right ventricular pressure estimates) and peak velocity measurements in valvular stenosis evaluation. This is particularly relevant when the UEAs are being used for imaging indications, especially because the threshold for the detection of microbubbles by Doppler is lower than that for imaging indications. When performing these measurements, the Doppler gain signals should be lowered from unenhanced echocardiography settings, to a level that reduces "microbubble noise" and improves the resolution of the Doppler profile. As emphasized in the 2008 guidelines, the most distinctly enhancing spectra should be measured at a lowered gain setting to reduce blooming artifact.

Key Points and Recommendations

1. VLMI multipulse imaging techniques with or without brief high-MI (flash) impulses to clear myocardial contrast should be used to image UEAs for RWM analysis (Video 1; available at www.onlinejase.com) and quantification of LV ejection fraction (LVEF; COR IIa, LOE B-R).
2. VLMI multipulse imaging techniques can also be useful for detecting MP (Videos 2–4; available at www.onlinejase.com) using brief high-MI flash impulses to clear myocardial contrast and subsequently analyzing myocardial replenishment kinetics and plateau intensity (COR IIa, LOE B-R).
3. Doppler-enhanced signals of tricuspid regurgitant jets can be obtained, especially if UEAs are being used for other imaging indications, and the jet was not visualized adequately without contrast. This also applies to enhancement of Doppler spectrum related to valvular stenosis, if needed. (COR I, LOE C-EO).
4. Manufacturers should provide users with information on the contrast-specific algorithms available on their systems and how to readily access them. This should include information on how to apply brief high-MI impulses (MI > 0.5) to clear myocardial contrast and enhance endocardial border delineation with these pulse sequence schemes. Table 4 displays the front-end location for VLMI imaging presets on the most recent versions of commercially available systems.

IV. CLINICAL APPLICATIONS

Since the 2008 ASE consensus statement,[1] numerous publications have reinforced existing applications or emphasized new applications for ultrasound enhancement.[16,18,23,26,27,39-68] This section will provide an update on these specific clinical applications and recommendations for their use.

IV.A. Update on Quantification of LV Volumes, LVEF, and RWM

According to the recent ASE/European Association of Cardiovascular Imaging recommendations for LV chamber quantification, volumetric measurements should be based on tracings at the interface of the compacted myocardium and the LV cavity.[69] However, trabeculations in the apical region, as well as artifacts from adjacent lung tissue and noise, can make it difficult to track this interface. After injection of ultrasound contrast agent, the opacified blood in the left ventricle fills the spaces among the LV trabeculations up to the compacted myocardium, allowing more accurate and reproducible tracings to be performed. All three contrast agents commercially available for LVO have been extensively evaluated in large multicenter trials.[2-4]

LV Volumes. Defining normal values for LV size is important for prognosis in a spectrum of clinical diagnoses, including cardiomyopathy and

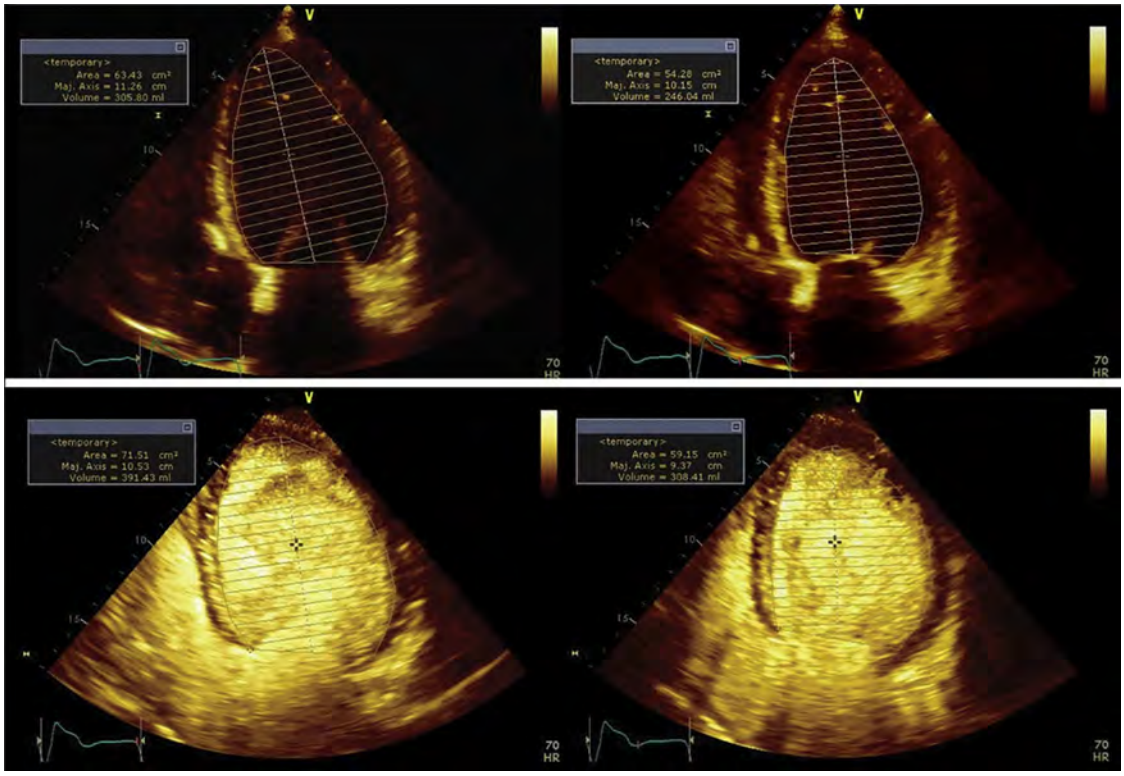

Figure 1 Differences in end-diastolic and end-systolic volumes observed in the same patient without contrast (*top*) and with UEAs and low-MI imaging (*bottom*). *Top row*, *left* to *right*: Precontrast LV quantification of end-diastolic volume (306 mL) and end-systolic volume (246 mL) for estimation of LVEF. *Bottom row*, *left* to *right*: Postcontrast LV quantification of end-diastolic volume (391 mL) and end-systolic volume (308 mL) for estimation of LVEF. A marked increase in volume size is noted after contrast.

valvular heart disease. Quantification of LV volumes is not a straightforward task and can depend on many factors, including populations studied and imaging methods. Current ASE guidelines for cardiac chamber quantification provide recommended standards for reporting LV internal diameters derived from the parasternal long-axis view, LV volumes by a biplane method, and normalization to body surface area[69]; use of UEAs is advised if this information cannot be readily obtained because of the poor quality of endocardial visualization. LV internal dimension measurements may underestimate the degree of LV enlargement compared with volume determination by biplane contrast.[70] Furthermore, unenhanced two-dimensional (2D) echocardiography may underestimate LV volumes because of foreshortening, exclusion of the portion of the left ventricle within noncompacted trabecular surfaces, and inadequate visualization of the endocardium. Use of UEAs may overcome these technical errors by allowing the true longitudinal axis of the left ventricle to be measured, as well as enabling accurate tracing of endocardial borders by detection of intratrabecular blood volume and clear delineation of the endocardial border (Figure 1), resulting in a closer correlation with cardiac magnetic resonance imaging (CMRI). LV volumes measured with unenhanced echocardiography are also consistently smaller than those derived from CMRI.[40] In a recent multicenter study, end-diastolic volume measurements determined by enhanced echocardiography were significantly larger than those without UEAs, irrespective of 2D or three-dimensional (3D) echocardiographic techniques.[40] However, there are currently no established values for normal LV volumes in enhanced echocardiography, as enhanced studies in large populations without cardiac disease or indications for contrast echocardiography are not feasible. An early study examining baseline prechemotherapy echocardiograms on female patients with breast cancer classified 51% of contrast-enhanced end-diastolic volume as abnormal, even though LV dimensions were within the normal range by unenhanced 2D volume measurements.[70] To account for this change in the normal range when using UEAs for volume measurements, the authors proposed an end-diastolic volume upper limit cutoff of 83 mL/m^2 for women and 98 mL/m^2 for men.[70] Using ±2 SDs from the mean of enhanced volumes as normal also resulted in better agreement with CMRI than that of noncontrast volumes. The Writing Group emphasizes the need for larger prospective studies to define ranges for LV volumes observed with UEAs and VLMI imaging.

Left Ventricular Ejection Fraction. The quantitative assessment of LVEF becomes particularly important when patients are considered for a defibrillator or cardiac resynchronization therapy, as well as in the follow-up of cardiotoxicity from chemotherapeutic agents or the evaluation of patients with valve disease for intervention (e.g., aortic and mitral regurgitation). In these circumstances, reproducibility is of critical importance. Several studies have demonstrated that when comparing unenhanced with enhanced cardiac ultrasound, and using CMRI as the gold standard, the accuracy of determination of LVEF was improved with UEA. Multicenter studies have confirmed that in comparison with unenhanced echocardiography, interobserver variability was significantly reduced with UEAs, resulting in similar intraclass correlation coefficients as seen with CMRI.[40,71] Although unenhanced 3D echocardiography has improved the reproducibility and reliability of serial ejection fraction measurements (as in the case of cancer chemotherapy), the use of UEAs in this setting has not further improved test-retest variability.[72] However, VLMI imaging techniques have not been available for 3D acquisitions.

Regional Wall Motion. Analysis of RWM is subject to significant interobserver variability. Inherently, wall motion is a subjective assessment without a gold standard and is in part dependent on image quality, highlighting the importance of being able to accurately detect the endocardium throughout systole. It is also important to note that visual wall motion assessment relies on evaluation of wall thickening, and thus both the endocardium and epicardium must be identified. A multicenter study has demonstrated that interobserver agreement for RWM was highest in patients who underwent enhanced echocardiography compared with unenhanced echocardiography and CMRI.[73] This same group of investigators found that UEAs significantly improved the agreement for RWM over nonenhanced echocardiography compared with CMRI.[40] In this study, 3D-enhanced echocardiography did not show any incremental value over 2D-enhanced echocardiography in the detection of RWM abnormalities. Similarly, the use of echocardiographic enhancement during stress has been shown to improve visualization of LV segments, interpretation confidence, sensitivity, and specificity in technically challenging and obese patients.[58] Although the Writing Group does not recommend UEA use where the heart cannot be imaged because of chest deformity or lung hyperexpansion, UEAs should be used for RWM analysis whenever the appropriate views can be obtained but endocardial border delineation is inadequate for interpretation.

Key Points and Recommendations

1. As per 2008 ASE guidelines, for routine resting echocardiographic studies, UEAs should be used when two or more LV segments cannot be visualized adequately for the assessment of LV function (LVEF and RWM assessment) and/or in settings in which the study indication requires accurate analysis of RWM. (COR I, LOE A).
2. A brief (5- to 10-frame) high-MI (0.8–1.2) "flash" impulse can be used with VLMI imaging to clear myocardium of contrast and improve endocardial border delineation for volume and ejection fraction measurements (COR IIa, LOE C-EO).
3. Ultrasound enhancement should be used in all patients in whom quantitative assessment of LVEF is important to prognosis or management of the clinical condition. VLMI and low-MI harmonic imaging techniques should be used to provide optimal LVO (COR I, LOE B-R).
4. LV volumes obtained by enhanced echocardiography are typically larger than those measured without UEAs, and therefore 2015 ASE chamber quantification guidelines should be applied with caution when determining normal ranges. Although the normal range for LVEF does not appear to be different, new reference ranges for end-diastolic and end-systolic LV volumes when using UEAs should be established.
5. As per section III of the 2014 ASE guidelines for sonographers,[38] a continuous infusion or a low volume (≤0.5 mL) bolus injection with slow (10–20 sec) saline flush is recommended along with VLMI imaging to minimize apical microbubble destruction and basal segment attenuation.

IV.B. Update on Intracardiac Abnormalities

There are specific areas in which prior guideline documents have recommended UEAs for intracardiac abnormalities. The 2016 ASE guidelines for the use of echocardiography in evaluation for a cardiac source of embolism recommend the use of UEAs "to assist in border definition and check for vascularization" of intracardiac thrombi or masses and consider as "potentially useful" the application of UEAs to aid in detection of left atrial and appendage thrombi (discussed later) and differentiation of avascular thrombi from vascular tumors.[74] The 2011 ASE clinical recommendations for multimodality cardiovascular imaging of patients with hypertrophic cardiomyopathy affirm that transthoracic echocardiography (TTE) combined with the IV injection of a UEA should be performed in patients with hypertrophic cardiomyopathy with suspected apical hypertrophy, to define the extent of hypertrophy and to diagnose associated potential complications of apical aneurysms and thrombi.[75] This document also outlines the specific protocol for septal perforator injections of diluted UEAs to delineate the perfusion territory of each perforator (section G.ii). Other clinical studies have been published that highlight these specific applications and support broader guidelines for UEA use.

Intracardiac Thrombi. Intracardiac thrombi pose serious clinical risks, including systemic embolization with potential catastrophic consequences; likewise, treatment with antithrombotic agents can also impose significant risk, and their use must be appropriately justified. Therefore, accurate detection and diagnostic management of cardiac thrombi is essential. Despite advances in other imaging modalities, echocardiography remains the initial tool for diagnosis and risk stratification in patients predisposed to developing cardiac thrombi. The use of UEAs facilitates LV thrombus detection by providing opacification within the cardiac chambers to demonstrate the "filling defect" appearance of an intracardiac thrombus (Video 5; available at www.onlinejase.com). Furthermore, perfusion echocardiography can provide an assessment of the tissue characteristics of identified LV masses by differentiating an avascular thrombus from a tumor, resulting in improved diagnostic performance of echocardiography.[38] Although delayed enhancement CMRI has the highest sensitivity and specificity for detection of LV thrombi, performance of echocardiography with a UEA is a more clinically feasible initial test. However, CMRI should be considered when a UEA with VLMI fails to detect an intracardiac thrombus but clinical suspicion persists.

Intracardiac Masses. Two-dimensional echocardiography is usually the primary initial diagnostic imaging modality offering real-time, high spatial and temporal resolution evaluation of cardiac masses. Although numerous echocardiographic criteria have been developed to define cardiac masses, diagnostic errors and misclassifications can lead to unnecessary surgery or inappropriate anticoagulation.[1] The judicious use of UEAs to characterize cardiac masses and integrate all the information to establish etiologies may potentially avoid these diagnostic errors. Intracardiac masses can be a normal variant of cardiac structure such as a false chord, accessory papillary muscle, or heavy trabeculation or can be pathologic such as thrombus, vegetation, or tumor. Any suspicious cardiac mass, when not clearly evident on baseline images, can be confirmed or refuted after injection of IV UEAs for better delineation of structures.[76] Just as with unenhanced echocardiography, off-axis images and longer loop acquisitions may be required to identify and characterize intracardiac thrombi or masses.

Echocardiographic perfusion imaging using VLMI with intermittent-flash (high-MI) technique has been demonstrated to characterize vascularity of cardiac masses and assist with the differentiation of malignant, highly vascular tumors from benign tumors or thrombi.[76] This characterization is supported by the qualitative and quantitative differences between the levels of perfusion (enhancement) in various types of cardiac masses and comparison with adjacent myocardium. The qualitative approach includes the visual inspection of rate of contrast replenishment within the mass following a high-MI impulse and descriptively categorized as lack of enhancement, partial or incomplete enhancement, or complete enhancement.[77] Most malignancies have abnormal neovascularization that supplies rapidly growing tumor cells, often in the form of highly concentrated, dilated vessels.[77] Thus, complete enhancement or hyperenhancement of the tumor (compared with the surrounding myocardium) supports the existence of a highly vascular tumor, which is most often malignant.[77] Stromal tumors, such as myxomas, have a poor blood supply and appear partially enhanced (Video 5, Figure 2; available at www.onlinejase.com), while thrombi or papillary

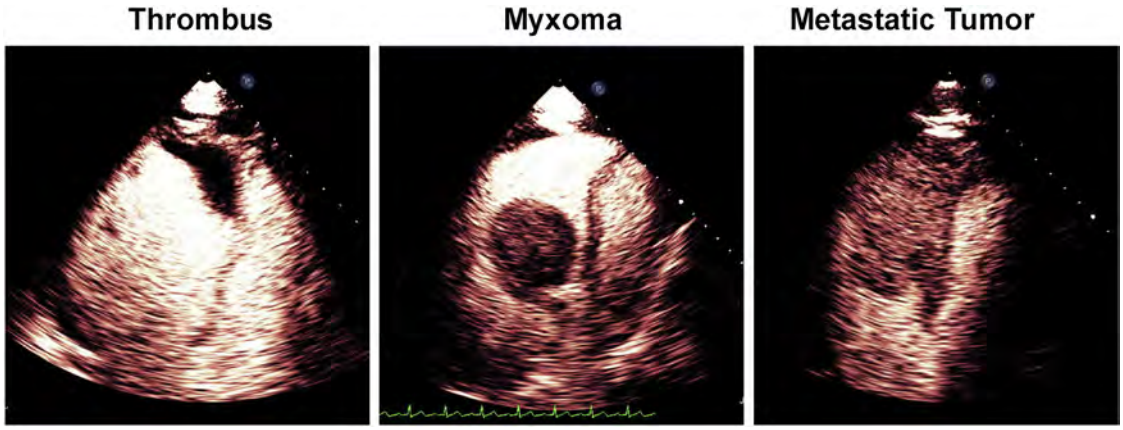

Figure 2 Modified apical four-chamber images of intracardiac masses in patients receiving continuous UEA infusion. All images were obtained at plateau intensity before a high-MI impulse. The *left panel* exhibits no enhancement, consistent with thrombus. The *middle panel* exhibits a small amount of enhancement (less than myocardial) and was a myxoma. The mass in the right ventricle in the *right panel* was hypervascular (similar to myocardial plateau enhancement) and was a metastatic renal cancer (see Video 5; available at www.onlinejase.com).

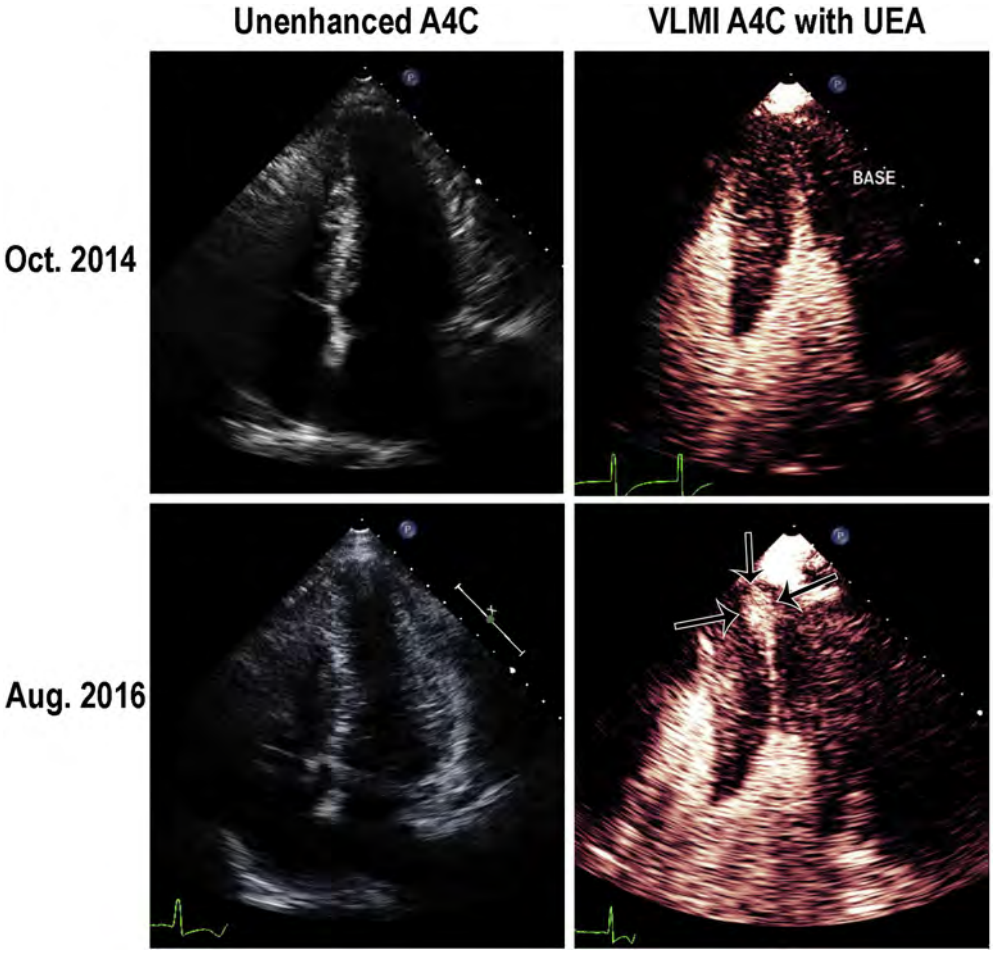

Figure 3 Apical four-chamber end-systolic images of a patient with apical hypertrophic cardiomyopathy. Unenhanced images (*left*) fail to delineate endocardial border, but VLMI images during a continuous infusion of a UEA (*right*) demonstrated apical hypertrophy in October 2014. Over approximately 2 years, VLMI imaging detected the interval development of an apical aneurysm. The patient subsequently had an implantable defibrillator placed.

fibroelastoma are generally avascular and show no enhancement.[78] The level of enhancement has been shown to correlate with the pathologic diagnosis or with resolution of the mass after anticoagulant therapy.[77] However, potential pitfalls exist that may contribute to the appearance of partial enhancement of avascular structures in the far field. Therefore, it is recommended that perfusion imaging

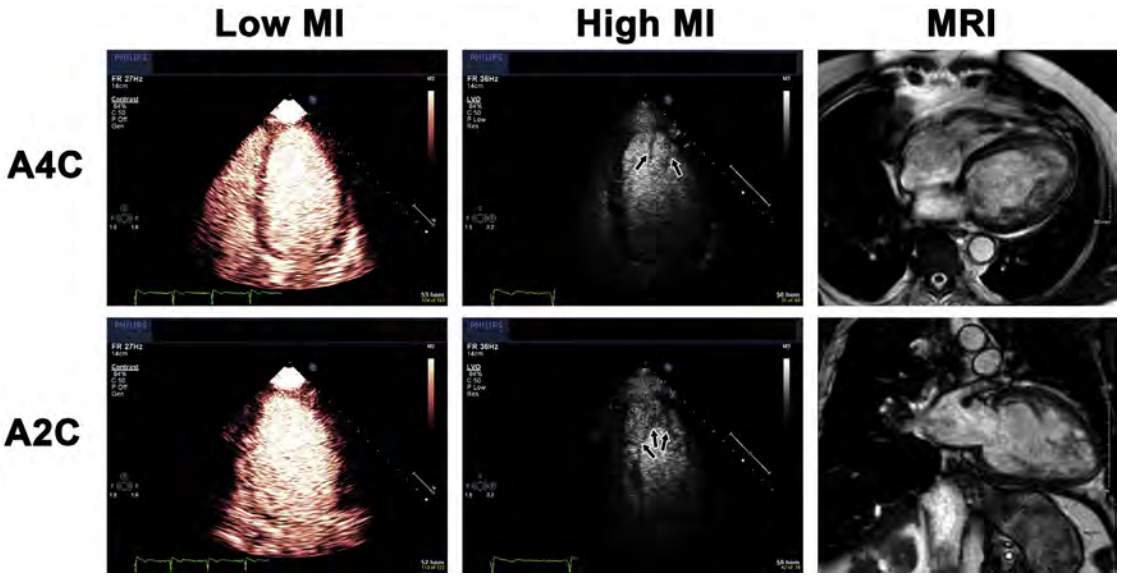

Figure 4 Apical four- and two-chamber (A4C and A2C) views at end-diastole in a patient with unexplained cardiomyopathy. VLMI imaging demonstrated LV cavity and myocardial opacification, but real-time B-mode harmonic imaging at a slightly higher MI (*middle*) resulted in destruction of trabecular myocardial microbubbles and better delineation of the noncompacted layer (*arrows*). The noncompaction thickness in this intermediate-MI real-time harmonic imaging mode correlated closely with that seen at magnetic resonance imaging (*right*).

be done in views that allow near-field visualization of microbubble replenishment following high-MI impulses. Several investigations since the 2008 ASE contrast document[1] have confirmed the differences in maximum acoustic intensity and mass-replenishing velocity following high-MI impulses during VLMI for various pathologies.[79,80]

Apical Abnormalities in Patients with Hypertrophic Cardiomyopathy. The apical variant is present in about 7% of patients with hypertrophic cardiomyopathy but may not be detected by routine TTE, because of incomplete visualization of the apex. 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 spade-like appearance of the LV cavity in diastole, with marked apical myocardial wall thickening, is clearly evident on enhanced images.[1] Complications associated with apical hypertrophy can also be readily visualized, such as apical aneurysm formation and thrombi (Figure 3, Video 6; available at www.onlinejase.com). The presence of an apical aneurysm has recently been associated with adverse outcomes, including arrhythmic events and thromboembolism.[81] However, some pitfalls can be encountered, leading to false-negative echocardiographic findings, as is the case in smaller apical aneurysms, or if contrast-specific imaging machine settings are not optimized, as was reported in a recent study comparing enhanced echocardiography with CMRI.[82] Because VLMI imaging permits better apical delineation, it is recommended that UEAs be routinely used with VLMI imaging in evaluating patients with hypertrophic cardiomyopathy (Video 6; available at www.onlinejase.com). Adjustment of the transmit focus to an apical position may reduce scan line density and UEA destruction, further improving apical image resolution.

Noncompaction Cardiomyopathy. Noncompaction of the myocardium is an uncommon but increasingly recognized abnormality that can lead to heart failure, arrhythmias, cardioembolic events, and death. 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. Enhanced echocardiographic studies may be helpful in identifying the characteristic deep intertrabecular recesses by showing microbubble-filled intracavitary blood between prominent LV trabeculations when LV noncompaction is suspected but inadequately seen by conventional 2D imaging (Figure 4). It may be useful to use an MI that is somewhat higher than VLMI (e.g., increase to 0.3–0.4) to better distinguish the myocardial trabeculations in the noncompacted myocardium from UEA presence within the deep recesses.[1,38] This higher MI at real-time frame rates destroys the low-velocity microbubbles within the trabecular myocardium before they can replenish, while the higher velocity intertrabecular microbubbles in the LV cavity can replenish, permitting better delineation of the noncompacted layer (Figure 4).

Post–Myocardial Infarction Complications. LV aneurysm, an often asymptomatic complication of a prior myocardial infarction, is a common apical LV abnormality. True aneurysms are characterized by thin walls and a dilated apex, which may be akinetic or dyskinetic and involve the full thickness of the ventricular wall. These findings are usually seen easily on unenhanced echocardiographic imaging. However, if the apex is not completely visualized, an apical aneurysm may go undetected until a UEA is used. LV pseudoaneurysm, free wall rupture, and post–myocardial infarction ventricular septal defects pose life-threatening risks to patients and can usually be detected by unenhanced echocardiography. However, patients may have suboptimal studies because of anatomy or position, or both, and clinical conditions (e.g., being supine and intubated in the critical care unit) that limit the attainment of an optimal view of the apex. UEAs may be essential in establishing the diagnosis, as well as detecting further associated complications, such as LV thrombus.[1]

Right Ventricular Assessment. Although agitated-saline enhancing agents can be used to visualize abnormalities in the right-sided chambers, the contrast effect is of short duration. When

persistent enhancement of the right ventricular endocardial borders is necessary, commercially available UEAs have been used to show various abnormalities of right ventricular morphology, including focal RWM abnormalities, tumors, and thrombi. The UEAs can also be used to distinguish these abnormalities from normal structures, such as prominent trabeculations or the moderator band.[1] In this setting, parasternal views, or a modified apical four-chamber window of right ventricle, may be optimal to place the right ventricle into the near field.

Atria and Left Atrial Appendage. UEAs have also been used to show anatomic features of the atria, especially the left atrial appendage, more clearly and can be useful in differentiating thrombi from artifacts, dense spontaneous echocardiographic contrast, or normal anatomic structures.[83] Differentiation of artifacts from thrombus is especially important in the setting of precardioversion transesophageal echocardiography (TEE). A prospective study of 100 patients undergoing precardioversion TEE demonstrated that UEAs provided improved identification of left atrial appendage filling defects and differentiation from artifacts, resulting in an increased level of confidence for thrombus exclusion before cardioversion.[83] Moreover, in another prospective case-control comparison study of 180 patients in atrial fibrillation undergoing cardioversion, no embolic events occurred in the group that was imaged with UEAs during precardioversion TEE, while three events occurred in a control group. The authors concluded that in patients with atrial fibrillation planned for cardioversion, contrast enhancement renders transesophageal echocardiographic images more interpretable, facilitates the exclusion of atrial thrombi, and may reduce the rate of embolic adverse events.[84] Specific MI settings were not provided in these studies, but it is likely that at frequencies used in TEE, an MI < 0.5 and harmonic mode will be optimal for UEA delineation.

Key Points and Recommendations for the Use of UEAs in Detecting LV Cavity Abnormalities and Intracardiac Masses

1. Ultrasound enhancement should be used in patients in whom LV thrombus cannot be ruled in or out with noncontrast echocardiography (COR I, LOE B-NR).
2. Ultrasound enhancement should be considered in patients in whom structural abnormalities of the left ventricle (noncompaction cardiomyopathy, apical hypertrophy and aneurysms) cannot be adequately assessed with noncontrast echocardiography (COR IIa, LOE B-NR).
3. Ultrasound enhancement should be used for ruling in or out an LV pseudoaneurysm (COR I, LOE B-NR).
4. Ultrasound enhancement with VLMI imaging should be used in the differential diagnosis of cardiac masses by assessing the vascularity of the mass (COR IIa, LOE B-NR).
5. Ultrasound enhancement should be considered during TEE whenever the atrial appendage has significant spontaneous contrast or cannot be adequately visualized with unenhanced imaging (COR IIa, LOE B-NR).

IV.C. Stress Echocardiography

Left Ventricular Opacification. LVO with low-MI harmonic imaging has been demonstrated to be integral in the achievement of more accurate and efficient stress echocardiographic testing.[85] The use of UEAs during both exercise and dobutamine stress echocardiography (DSE) improves sensitivity, specificity, and diagnostic accuracy to a greater extent in patients with suboptimal versus optimal imaging windows.[1] This improvement in accuracy has been attributed to the ability to visualize all regional wall segments, making it equivalent to the accuracy of optimal unenhanced studies in which all segments can be visualized.[16] In 839 consecutive patients undergoing stress echocardiography, the addition of UEAs with VLMI imaging during stress echocardiography improved endocardial border detection at rest and peak stress, yielding 99.3% efficacy in achieving diagnostic study quality,[86] thereby improving reproducibility and reader confidence in interpretation. This has translated into a significant impact on accuracy, especially when the unenhanced image confidence was low or there were more than two segments not well visualized without contrast.[85]

Decision algorithms in which contrast imaging enhancement is used when two or more segments are not adequately visualized, beginning at rest and repeated at peak stress, produce a cost savings with abnormal testing predicting mortality and adverse events. Compared with exercise electrocardiography (ECG) and nuclear testing, UEA use results in fewer downstream tests, which correlates with significantly lower costs.[68]

Although the VLMI multipulse sequence schemes were available on most manufacturing systems as detailed in the 2008 ASE consensus statement,[1] only recently have manufacturers begun using them for LVO. The VLMI techniques were initially designed for MP assessment, but their sensitivity for microbubble detection and complete apical cavity opacification without swirling artifact has improved stress LVO imaging. Both multicenter and prospective single-center studies have demonstrated the effectiveness of VLMI imaging to detect RWM abnormalities.[16,45,66] In addition to enhanced sensitivity and apical delineation, the VLMI techniques detect subendocardial wall thickening abnormalities that may otherwise go undetected if one were examining transmural wall thickening during demand stress.[42,66] The combination of LVO and subepicardial layer enhancement during replenishment following high-MI impulses helps delineate the subendocardium and analysis of wall thickening just at this location (Figure 5, Video 7; available at www.onlinejase.com). The integration of UEAs with VLMI imaging for the evaluation of wall thickening and ischemia into the routine evaluation of patients with left bundle branch block during DSE has been shown to improve the detection of CAD and independently predict mortality and cardiovascular events.[67]

On the basis of these studies, it is apparent that UEAs improve the diagnostic accuracy of RWM analysis at rest and during stress imaging. VLMI imaging appears to be optimal for RWM analysis, in that the added perfusion data assist in the differentiation of subtle wall thickening abnormalities due to subendocardial ischemia. This appears to be helpful in all coronary artery territories and may be especially helpful in segments that are frequently difficult to visualize (Figure 6, Videos 4 and 7; available at www.onlinejase.com). Because disease in a coronary artery territory may affect only one segment in any particular apical or parasternal view, the Writing Group recommends that UEAs be used for LVO whenever any segment cannot be adequately visualized.

Perfusion Imaging during Inotropic or Exercise Stress. MP imaging has been used in a variety of circumstances for the assessment of myocardial ischemia and viability. VLMI imaging with IV infusions or small bolus injections of UEAs has been used to examine myocardial blood flow and volume at frame rates of 20 to 30 Hz. This has been termed real-time MCE (RTMCE). Brief high-MI impulses are administered to clear myocardial contrast, following which replenishment is analyzed on the end-systolic images (Videos 8 and 9; available at www.onlinejase.com). This technique has been performed clinically

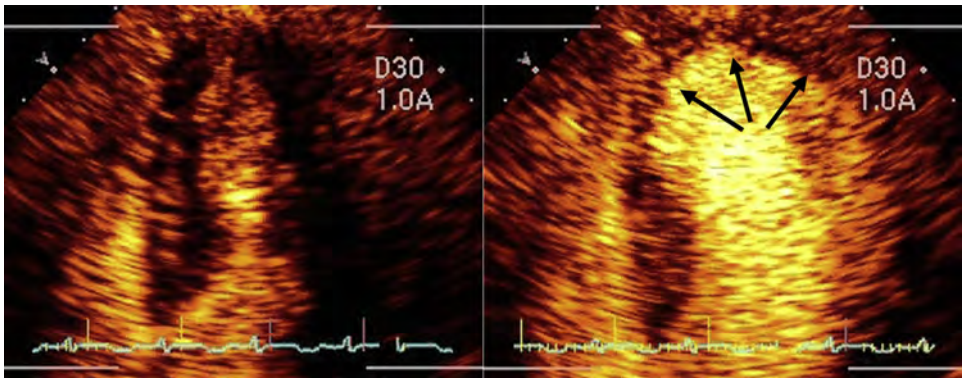

Figure 5 Subendocardial perfusion defect and subendocardial wall thickening abnormality (*arrows*) that is not seen when contrast was opacifying only the LV cavity and not the subepicardium (*left*). During myocardial contrast replenishment, the subendocardial perfusion defect (*arrows*) delineates the subendocardial wall thickening abnormality (see Video 7; available at www.onlinejase.com).

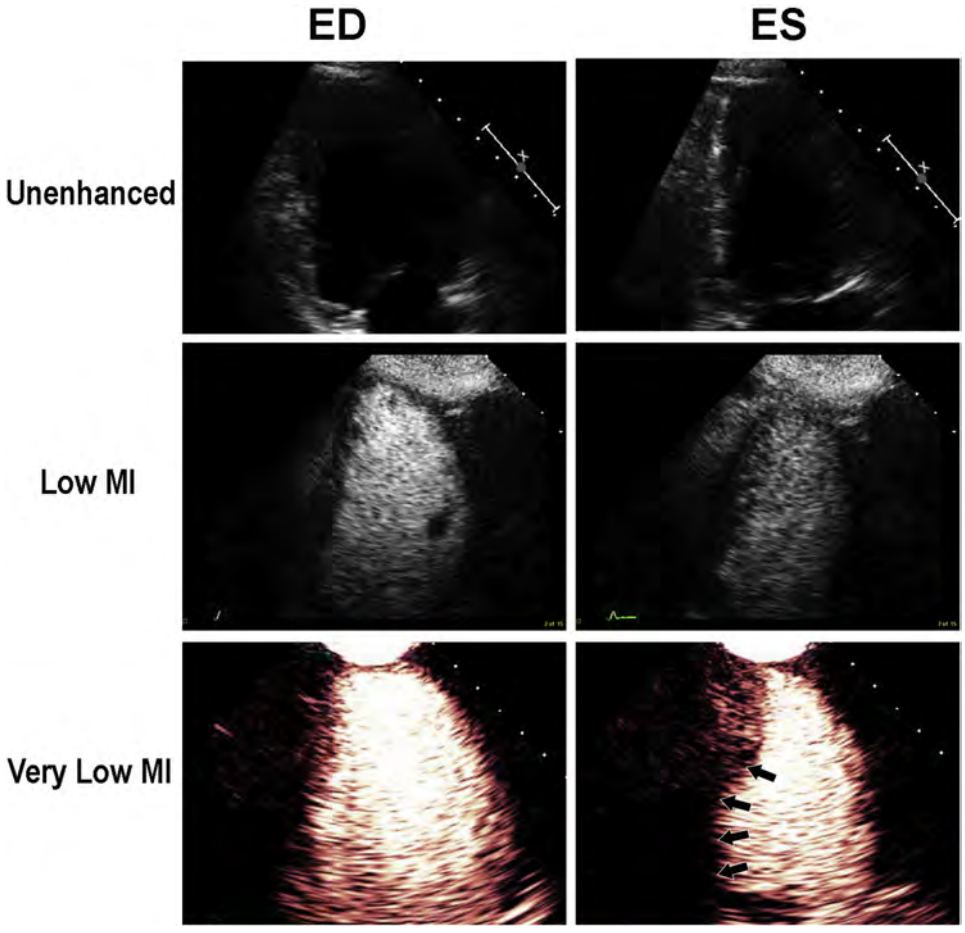

Figure 6 End-diastolic (ED; *left*), and end-systolic (ES; *right*) in the apical two-chamber view, demonstrating how only VLMI imaging with UEAs can completely delineate a basal to mid inferior wall thickening abnormality. Because VLMI imaging is done with power modulation, fundamental nonlinear responses are detected, resulting in less basal segment attenuation compared with low-MI imaging (*middle*) which are attenuated because they are harmonic frequency signals. See Video 4, available at www.onlinejase.com.

in thousands of patients during dobutamine stress or with treadmill or bicycle exercise.[16,42,45,46,49,57,65,66]

In the setting of DSE, perfusion analysis has improved CAD detection compared with wall motion analysis alone. The improvement appears to be related to the ischemic cascade, in which perfusion abnormalities have been shown to occur before wall motion abnormalities during demand ischemia.[34] As discussed in the previous section, another factor leading to improved sensitivity with VLMI imaging is the detection of subendocardial wall thickening abnormalities when using perfusion enhancement (Figure 5). This has been evident primarily in DSE,[42,45,66] where transmural wall thickening may appear normal despite the existence of a subendocardial wall thickening abnormality unmasked by the subendocardial perfusion defect (Video 7; available at www.onlinejase.com).

The 20- to 30-Hz frame rates with VLMI imaging have permitted sonographers and physicians trained in basic echocardiography to adapt to this technique, whether they are using UEAs to enhance RWM analysis, assess global systolic function, or analyze perfusion. The higher spatial resolution of perfusion echocardiography, compared with radionuclide imaging or positron emission tomography, has permitted improved detection of ischemia at rest and during stress. It may also be useful in patient populations with resting nonischemic wall motion abnormalities such as ventricular paced rhythms or left bundle branch block.[48] Adding perfusion information to RWM analysis has resulted in better defining the extent of CAD that exists[34] and is better than RWM analysis alone in identifying those at risk for subsequent cardiac events.[45]

Perfusion abnormalities during demand stress have been correlated with fractional flow reserve measurements using invasive hemodynamics in patients with intermediate angiographic stenosis between 50% and 80% in diameter.[65] Here the correlations are not good and reflect differences in what the two techniques are measuring. Fractional flow reserve is determined by measuring a pressure gradient across a given stenosis during hyperemic stress in the catheterization laboratory and does not take into account the impact of capillary resistance, which has been shown to be the major regulator of coronary blood flow during stress.[87] Because RTMCE measures capillary blood velocity and blood volume, stress-induced abnormalities may exist before detection of significant hyperemic pressure changes across a stenosis in the 50% to 80% range. These differences appear to be clinically relevant,[65] and further investigation into their prognostic significance is needed.

Since the publication of the 2008 ASE contrast document,[1] the incremental value of MP imaging over wall motion analysis alone in predicting patient outcomes has been demonstrated with bicycle exercise echocardiography,[46] treadmill exercise echocardiography,[45] and DSE.[16,45] This includes RCTs comparing conventional stress echocardiography (in which UEAs were used only for the current FDA-approved indication) with RTMCE. In each of these settings, delayed replenishment of contrast during a continuous infusion of microbubbles was seen in a significant percentage of patients in the absence of RWM abnormalities and appeared to be independently predictive of subsequent death and nonfatal myocardial infarction.

Perfusion Imaging during Vasodilator Stress. Since the publication of the last 2008 ASE consensus statement regarding the use of UEAs in the context of echocardiography,[1] many pertinent studies have reported on feasibility, safety, diagnostic and prognostic accuracy of RTMCE in the assessment of MP imaging, specifically during vasodilator stress echocardiography, strengthening the evidence toward the use of such vasodilator stress modality in conjunction with RTMCE.[27,39,41,43,47,48,50-53,55,56,64] Vasodilator stress perfusion imaging appears to provide equivalent information for detection of CAD compared with inotropic stress, with advantages of rapid performance and possibly better image quality due to the lower heart rate (often not exceeding 100 beats/min) and less translational cardiac movement (Figure 7). However, conventional detection of stress-induced RWM abnormalities may in some cases be less sensitive because the mode of stress does not depend on myocardial oxygen demand. Several vasodilators have been used in studies with RTMCE, namely, adenosine,[16,43,47,50,51] dipyridamole,[26,27,41,43,48,52,53,55] and, more recently, regadenoson.[54,64] Adenosine and dipyridamole are the most commonly used vasodilators for perfusion imaging. Both agents act nonselectively directly or indirectly to activate all four adenosine receptor subtypes (A1, A2A, A2B, and A3). This can result in chest pain, mild dyspnea, hypotension, bronchospasm, and, rarely, reversible atrioventricular nodal block. Regadenoson is a potent selective A2A agonist, administered as a 400-μg IV bolus, with rapid onset of action (within 30 sec) and adequate duration of action to allow sufficient time for image acquisition (up to 4 min) with less severe side effects, and it may evolve to be one of the vasodilators of choice for perfusion imaging (Figure 8). Information from perfusion data is equivalent for all these vasodilators, and therefore the choice for each can be tailored on the basis of local availability, cost, side effects, and perceived practical advantages or disadvantages.

Some vasodilator stressors can be used at different dosages, depending on whether only perfusion or also wall motion stress information is desired. For example, dipyridamole may be administered over 4 min to a total dose of 0.56 mg/kg to achieve perfusion assessment, while a longer infusion and a higher dose are required to accurately detect RWM abnormalities with this technique.

Large multicenter trials comparing RTMCE with single-photon emission computed tomography (SPECT) using the above pure vasodilatory dose of dipyridamole for the detection of CAD have been performed.[27,41] The first such trial showed equivalent sensitivity and specificity for the detection of CAD, but in the latter trial, which was larger with all images read blindly at other centers, and when using coronary angiography as a reference standard, the sensitivity of MCE was superior to that of SPECT. The basis of superior sensitivity appears to be that (1) MCE has better spatial resolution compared with SPECT,[48] and (2) vasodilator SPECT assesses only capillary blood volume, while MCE detects both capillary blood volume and capillary velocity,[88] the latter being a more sensitive marker of CAD. Preliminary retrospective studies examining the prognostic power of vasodilator stress RTMCE have demonstrated enhanced predictive value compared with SPECT.[39] For simultaneous evaluation of perfusion and function during vasodilator stress, a high dose of vasodilator (0.84 mg/kg over a 6-min infusion) is required. High-dose dipyridamole (with or without atropine coadministration) for RWM assessment for the diagnosis and prognosis of CAD has been well established on the basis of more than two decades of published studies, encompassing several thousands of patients (mostly European studies). Thus, when using RTMCE for simultaneous assessment of perfusion and function, experience with high-dose dipyridamole predominates. In this setting, it has consistently been shown that perfusion analysis improves overall accuracy for CAD detection compared with RWM analysis alone, with an even greater diagnostic benefit for the detection of angiographically intermediate (50%–70%) stenosis. The accuracy benefit is due mainly to an increase in sensitivity. Similar to demand stress, the improved sensitivity appears to be related to the ischemic cascade.[6] Furthermore, in specific patient populations with resting nonischemic wall motion abnormalities, such as left bundle branch block,[48] RTMCE has permitted improved detection of ischemia compared with radionuclide imaging and thus may be particularly useful in this setting, as well as in paced rhythm. Adenosine and regadenoson are both very potent vasodilators, and their accuracy in the induction of ischemia-related RWM abnormalities for the detection of CAD appears to be similar.[47,54]

From a prognosis standpoint, single-center studies have clearly demonstrated the incremental value of dipyridamole[55,67,71] and, in one study, adenosine[89] MP imaging over RWM analysis alone in the prediction of combined cardiac end points. In one study following >1,000 contemporary patients for >2 years, hard cardiac events (death or myocardial infarction) could also be better predicted than with RWM assessment alone.[55,67] In each of these settings, delayed replenishment of contrast during slow bolus or continuous infusion of UEAs was seen in a significant percentage of patients in the absence of RWM abnormalities and appeared to have independent prognostic value for prediction of subsequent death and nonfatal

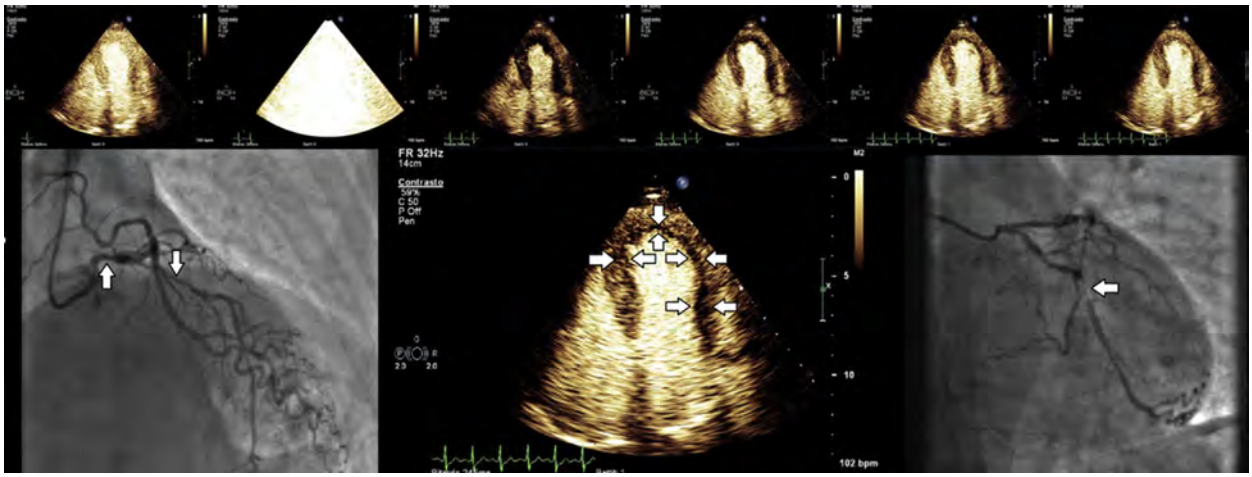

Figure 7 Demonstration of inducible anterolateral and apical perfusion defects (*arrows*) during dipyridamole stress RTMCE (*bottom middle*). The *top row panels* demonstrate the delay in replenishment in these segments following the high-MI flash impulse (*top second*). The corresponding angiogram (*bottom left and right*) demonstrates angiographic lesions in the left anterior descending and left circumflex coronary artery territories (*arrows*). See Video 10, available at www.onlinejase.com.

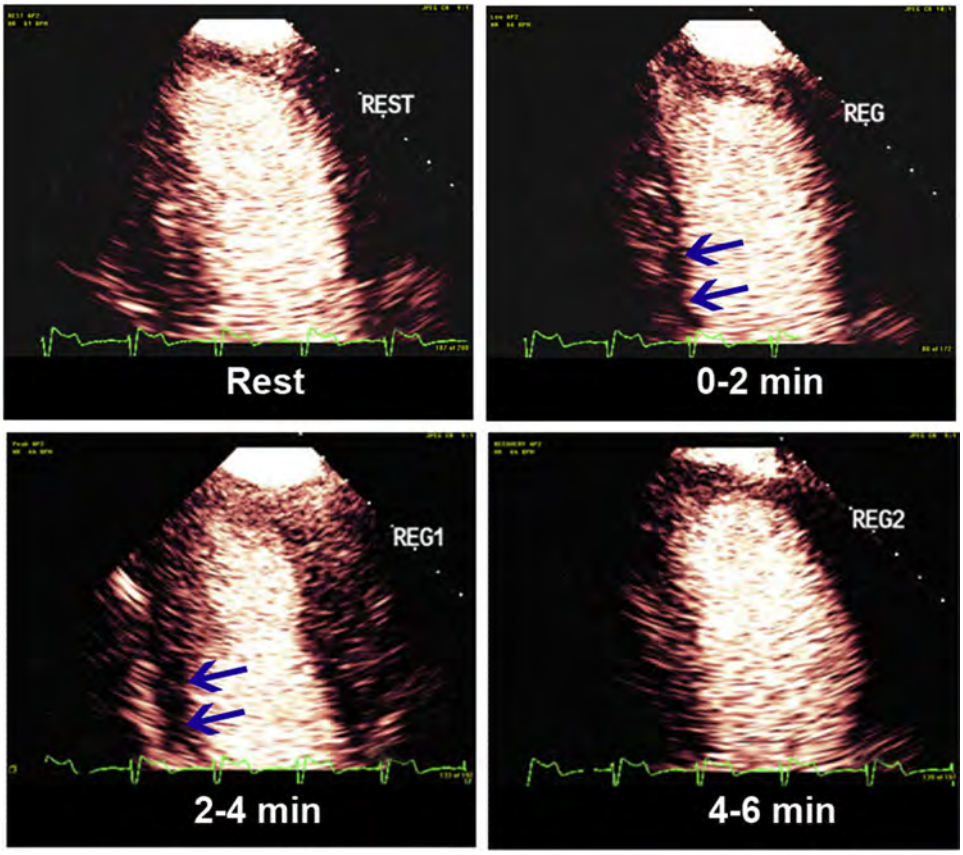

Figure 8 Demonstration of an inducible basal to mid inferior subendocardial perfusion defect at 0 to 2 and 2 to 4 min (*arrows*) following a 400-μg regadenoson bolus. *REG*, Imaging within 2 minutes of regadenoson bolus; *REG1*, imaging at 2-4 minutes after regadenoson bolus; *REG2*, imaging at 4-6 minutes after regadenoson bolus.

myocardial infarction. Five-year follow-up data in >1,300 patients following high-dose dipyridamole perfusion stress echocardiography have demonstrated that incremental prognostic information is obtained when combining MP with RWM analysis.[90]

When using vasodilator stress, the use of high-MI flash-replenishment technique is essential and likely more important than during demand stress, when perfusion defects may more easily become apparent even when not taking advantage of such flash-replenishment technique, because of significantly increased oxygen consumption. RTMCE using vasodilator stress has been evaluated with quantitative techniques, allowing the determination of myocardial blood flow and its stress/rest ratio (blood flow reserve) and has been found comparable with alternative techniques, although there is some controversy regarding the feasibility of this technique.[43,44,51]

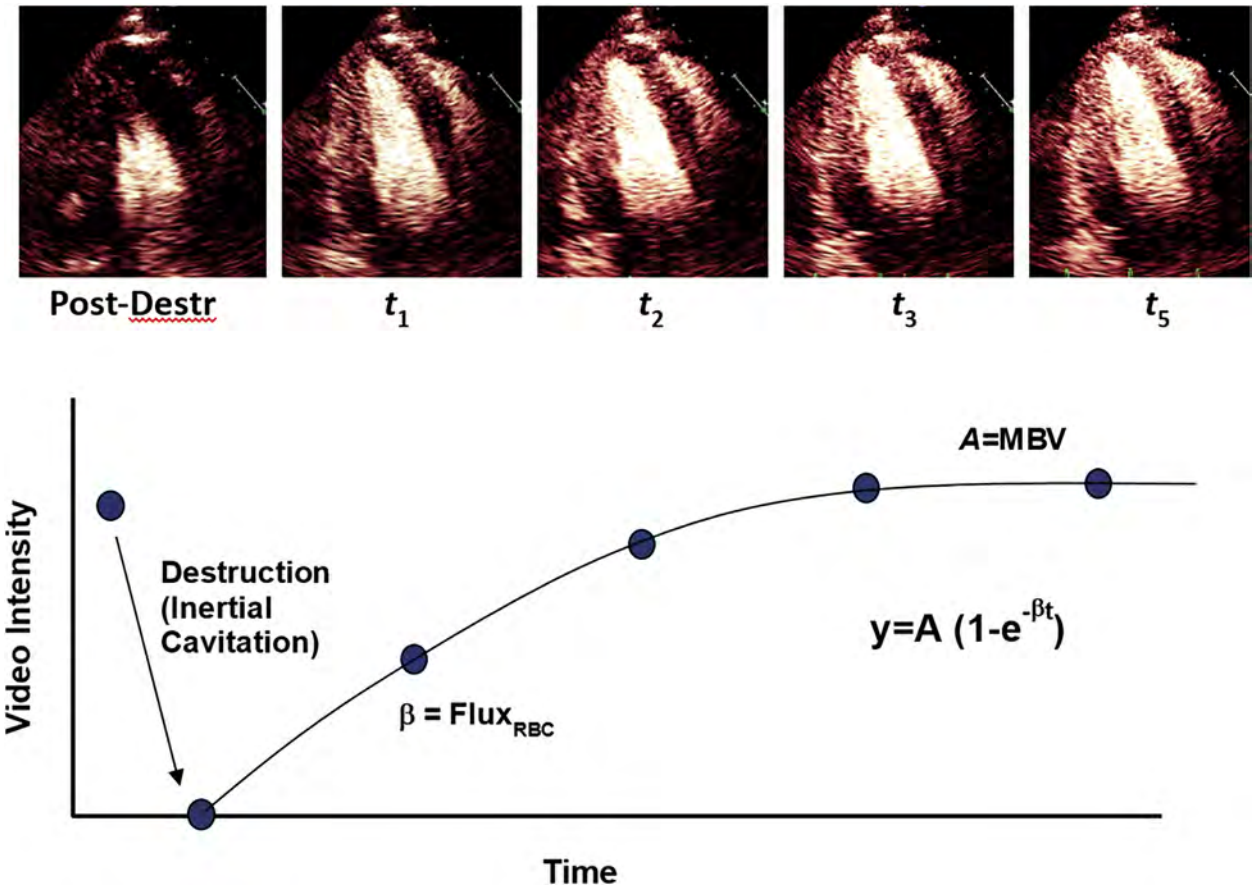

Figure 9 Illustration of myocardial contrast echocardiographic perfusion imaging sequence. The first image after the destructive pulse series illustrates complete elimination of contrast signal from the myocardium. Subsequent end-systolic frames (t_n) demonstrate progressive increase in myocardial intensity due to replenishment of microbubbles into the myocardial microcirculation. The graph illustrates the kinetic modeling used to derive the red blood cell flux rate ($Flux_{RBC}$) from the rate constant and the MBV from the plateau intensity (A). *Post-Destr*, End systolic image immediately after a high mechanical index impulse.

Visual qualitative analysis is more readily learned and less labor intensive (Figures 7 and 8, Video 10; available at www.onlinejase.com). The following rule of thumb permits interpretation: resting replenishment with a 2D echocardiographic transducer should be within 5 sec following a high-MI flash impulse and within 2 sec during stress (Videos 6 and 7; available at www.onlinejase.com).

Perfusion Quantification. When performing myocardial contrast echocardiographic perfusion imaging, there are situations in which the presence of perfusion in a binary "yes or no" fashion is sufficient, as when assessing the efficacy of reperfusion therapy for myocardial infarction or when evaluating the presence of myocardial viability. For these applications, one needs only to spatially evaluate the presence or absence of an intact microvasculature.[91,92] Quantitative assessments of myocardial blood flow and blood volume with MCE have been performed with bolus injections and continuous infusions of UEAs. Techniques for measuring the first pass of contrast agents after rapid bolus injection are used with other forms of noninvasive imaging and have been applied to MCE.[93] However, this approach is not recommended for MCE, because it is not possible to (1) image the entire heart during the first pass of contrast or (2) adequately account for bolus spreading during venous-to-systemic transit. Accordingly, perfusion imaging approaches have been developed specifically for MCE that are based on measuring the two main parametric elements of perfusion: (1) the number of microvascular units actively perfused at any time (microvascular blood volume [MBV]) and (2) the flux rate of blood through these microvascular units.[94] The measurement of these parameters relies on the unique ability to influence microbubble contrast integrity with ultrasound energy.[94,95] High-MI impulses that are >0.8 destroy microbubbles within the microcirculation, thereby eliminating their signal enhancement. The localized time-intensity analysis of microvascular reentry of microbubbles can be used to assess the rate and extent of microbubble signal replenishment, reflecting microvascular flux rate and MBV, respectively (Figure 9). It is recommended that this procedure be performed using (1) continuous infusions of microbubbles to allow a stable steady-state concentration of microbubbles in the blood pool, (2) only a few high-power "flash" frames (to avoid influencing blood pool concentration), and (3) only end-systolic frames for analysis (to eliminate signal from large intramyocardial vessels).[96,97] It is recognized by the Writing Group that small bolus injections of UEAs with slow saline flushes also can create a period of time following each injection during which steady state kinetics apply and have been effectively used in clinical studies to examine signal replenishment and MBV.[53,55] Background-subtracted intensity data can be fit to an exponential equation: $y = A(1 - e^{-\beta t})$, where y is the video intensity at any time t after the "flash" impulse, A is the plateau signal intensity

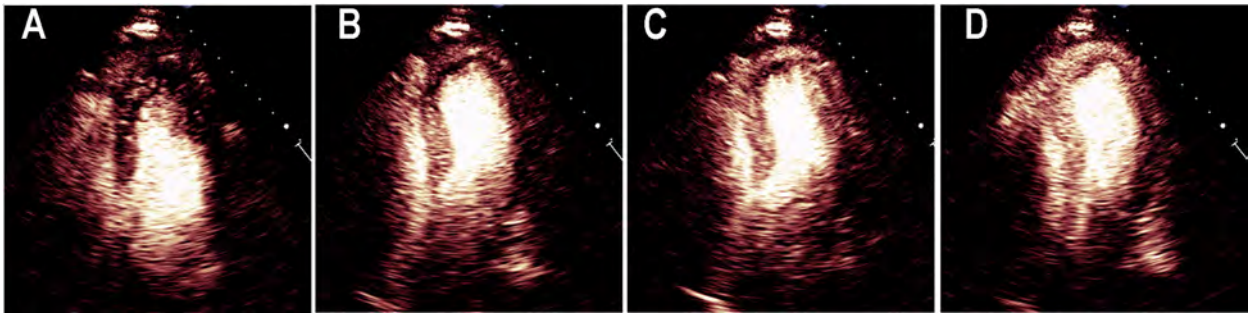

Figure 10 An example of a distal septal, apical, and distal lateral perfusion defect detected at end-systole, which is primarily evident during the replenishment phase following the high-MI flash impulse. **(A)** Immediate post-high MI impulse. **(B,C)** Early and late replenishment phases. At plateau intensity **(D)** at 5 sec following the high-MI flash impulse, the defect is no longer apparent. The basal anterolateral segment is most likely exhibiting attenuation.

reflecting relative MBV, and the rate constant β (sec^{-1}) reflects the flux rate of microbubbles through the microcirculation.[94] The product of blood volume and blood velocity ($A \times \beta$) provides a semiquantitative index of myocardial blood flow, whereas absolute blood flow can be derived by normalizing the A value to the blood pool signal to derive absolute MBV.

Quantitative analysis of blood flow or flow reserve has been validated against positron emission tomography, quantitative coronary angiography, Doppler flow wire, and SPECT.[51,98-100] It is generally recognized that the β value has better discriminatory value for detecting ischemia than the A value because of greater likelihood for artifacts when measuring A value (e.g., attenuation) and earlier perturbation of β in the course of disease (Figure 10).[101] Full quantitative assessment of MP with parametric mathematical analysis described above generally involves drawing large regions of interest that are based on either major coronary artery perfusion territories or recommended myocardial segmentation models. An important limitation is that a small area of severe ischemia within a segment may result in identical quantitative data as a larger region of more modest ischemia. Accordingly, it is recommended that quantitative data be accompanied by a qualitative assessment of the spatial extent of perfusion abnormalities, in terms of both the number of segments involved and the transmural versus subendocardial localization of flow abnormality.

Studies that have used quantitative or semiquantitative stress-rest MCE for the detection of CAD have demonstrated good diagnostic performance compared with angiography or other noninvasive stress imaging,[100-102] with a meta-analysis demonstrating sensitivity and specificity both in excess of 80%.[43] For patients with heart failure with reduced LVEF, quantitative MCE has been shown to be able to differentiate ischemic from nonischemic etiology.[103] Quantitative MCE also provides prognostic information in patients with ischemic heart disease with known or suspected CAD and normal LV function that is superior to that of qualitative perfusion analysis[89] and has been used for the evaluation of microvascular dysfunction in nonischemic and hypertensive cardiomyopathy, stress cardiomyopathy, and in patients with chest pain and positive stress testing but no obstructive CAD on coronary angiography.[62,104-106]

For the detection of CAD, a plateau intensity ratio (stress/rest) has not been useful for disease detection, but a β ratio or $A \times \beta$ ratio ≥ 2 appeared to have consistent predictive value in differentiating normal from abnormal myocardial blood flow reserve.[43] It is unknown whether this has predictive value in detecting microvascular abnormalities that are not due to epicardial CAD.

Key Points and Recommendations for Stress Echocardiographic Imaging with UEAs

1. UEAs should be used whenever adequate segmental visualization within any coronary artery territory cannot be achieved with resting unenhanced echocardiography (COR I, LOE A).
2. VLMI imaging is the preferred imaging mode and should be used with intermittent flash high-MI impulses (five to 15 frames at an MI of 0.8–1.0) to achieve homogeneous LVO and analysis of RWM (COR IIa, LOE B-R).
3. Continuous 3 to 5 mL/min infusions of dilute UEAs (3%–5% for Definity, 10% for Optison) or small bolus injections (0.1–0.2 mL for Definity, 0.3–0.5 mL for Lumason or Optison) with slow 5- to 10-mL saline flushes over 10 sec should be used to reduce acoustic shadowing and permit steady-state concentrations of microbubbles during image acquisition (COR I, LOE EO).

Recommendations 4 to 7 pertain to those individuals who have received recommended training in perfusion imaging techniques with UEAs

4. Although perfusion imaging with UEAs is off label, the detection of myocardial ischemia and viability can be enhanced when used in the correct setting by trained personnel.
5. If performing MP imaging, VLMI perfusion imaging should be used during demand stress using real-time high-MI flash replenishment technique for simultaneous perfusion and wall motion assessment (COR IIa, LOE B-R).
6. Perfusion analysis combined with RWM analysis using RTMCE should be considered during DSE to maximize the sensitivity and accuracy of the study for the detection of CAD and prediction of clinical outcome (COR IIa, LOE B-R).
7. Standard (0.56 mg/kg) or high-dose (0.84 mg/kg dipyridamole) vasodilator stress RTMCE should assess both MP and RWM to maximize sensitivity for the detection of CAD (COR IIa, LOE B-NR).
8. Adenosine and regadenoson stress should be performed with RTMCE to analyze both RWM and MP to maximize test sensitivity and specificity (COR IIa, LOE B-NR).
9. When homogeneous myocardial contrast is observed following an IV infusion or small, repetitive bolus doses of IV UEA, a flash high-MI impulse should be designed and adjusted to clear myocardium of contrast signals without excessive cavity microbubble destruction. The high-MI impulse should be 0.8 to 1.2. The number of flash frames should be adjusted to clear myocardial contrast while minimizing cavity destruction.
10. The replenishment for a 2D imaging plane should be uniform and within 5 sec under resting conditions and within 2 sec in a constant imaging plane during any form of stress imaging. Figure 11 demonstrates normal resting and demand stress replenishment following high-MI impulses. Figures 12 and 13 are examples of inducible MP defects in different coronary artery territories during dobutamine stress.
11. Quantitative MCE appears to have additional value over visual analysis in detecting myocardial blood flow abnormalities due to significant CAD but requires dedicated software capable of analyzing myocardial replenishment kinetics at end-systole following brief high-MI impulses. It is not recommended for clinical application until usable and readily available software is available on commercially available systems. The Writing Group recommends that all vendors develop quantitative software on their systems for analyzing replenishment rates and plateau intensities following high-MI impulses within any chosen region of interest.

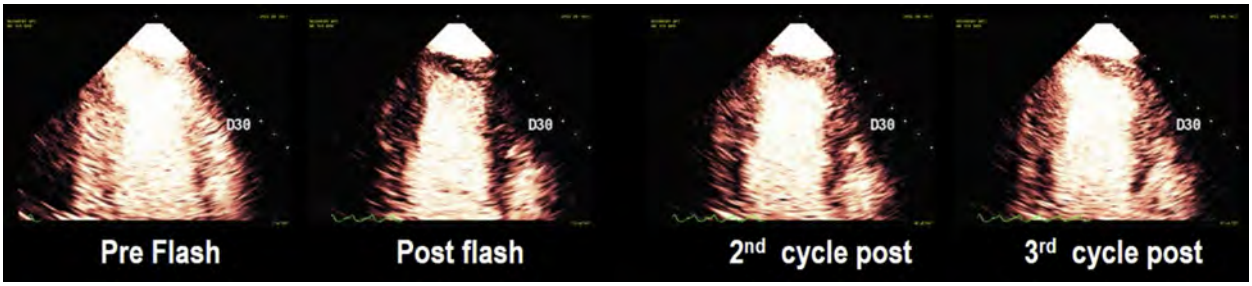

Figure 11 An example of stress end-systolic perfusion assessment during dobutamine stress RTMCE. Note that visual replenishment at end-systole occurs within 2 sec, which in this case is the third cardiac cycle after the high-MI impulse. Note a small subsegmental amount of basal inferior and basal anterior attenuation.

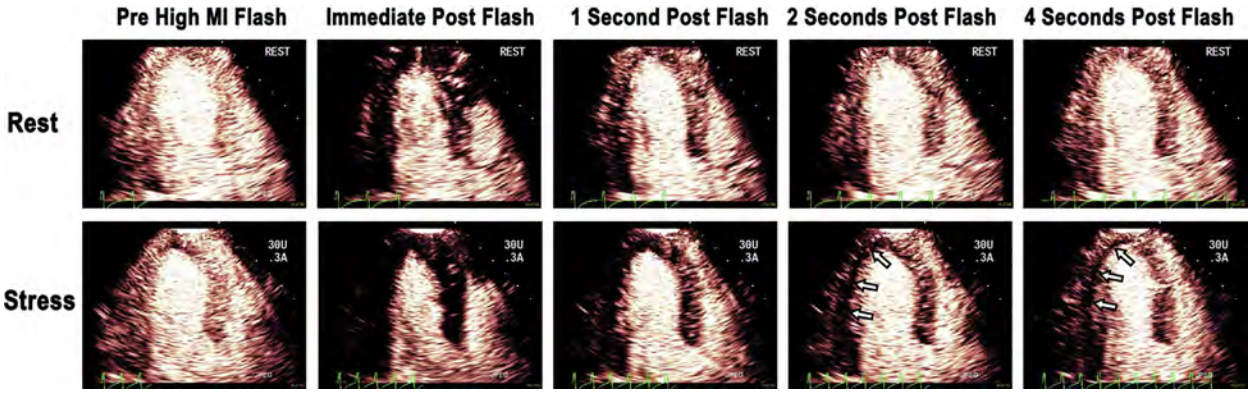

Figure 12 An example of a stress-induced perfusion defect in the left circumflex coronary artery territory (*arrows*). Note that end-systolic replenishment within the basal to mid inferolateral segments in the apical long-axis window is normal under resting conditions but delayed (*arrows*) during dobutamine stress imaging.

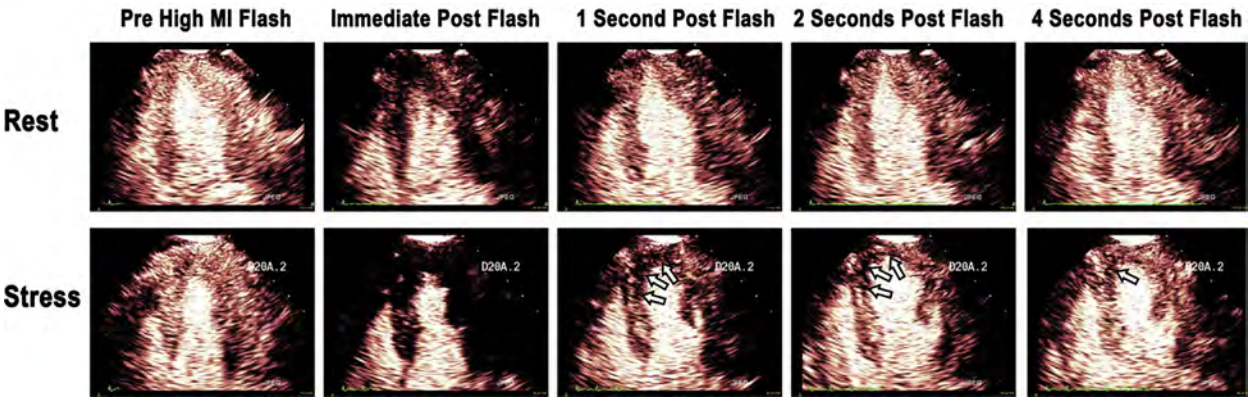

Figure 13 An example of a stress-induced perfusion defect in the left anterior descending coronary artery (LAD) territory (*arrows*). Note that end-systolic replenishment within the LAD territory in the apical four-chamber window is normal under resting conditions but delayed in the LAD territory (*arrows*) during dobutamine stress imaging.

IV.D. Vascular Imaging: Carotid, Femoral, Aortic, and Endografts

The use of UEAs for vascular imaging continues to grow rapidly (Table 5), including imaging of the carotid arteries, peripheral arteries, aorta, vascular grafts, and endovascular grafts.[107,108] Similar to cardiac applications, microbubbles can act as blood pool–enhancing agents to allow better visualization of vascular structure and flow (by B-mode grayscale imaging and color and spectral Doppler techniques), as well as perfusion in the context of imaging the vasa vasorum, atherosclerotic plaque neovascularization, and peripheral muscle perfusion.

Carotid Artery. In the majority of cases, UEAs are not required for standard ultrasound imaging of the carotid artery to determine stenosis severity. However, when ultrasound imaging is suboptimal, contrast opacification of the carotid artery lumen may be useful to better delineate plaques and ulcerations and help determine lesion severity. Specifically, UEAs are useful in select cases to differentiate a severely stenotic lesion from complete carotid occlusion (Video 11; available at www.onlinejase.com), thus affecting patient management.[109,110] Data continue to emerge on the utility of UEAs for assessing the vasa vasorum and carotid plaque

Table 5 Current and emerging vascular applications

Carotid artery	Luminal opacification to better delineate plaque characteristics, including ulceration and luminal patency (absence of complete occlusion)
	Evaluation of the vasa vasorum and carotid plaque neovascularization (emerging)
Femoral artery	Identification of flow into femoral artery pseudoaneurysms and guidance of percutaneous thrombin occlusion
PAD	Quantification of skeletal muscle perfusion and flow reserve in patients with PAD (emerging)
Aortic pathology and grafts	Identification of intimal flap in cases of suspected aortic dissection, and delineation of true and false lumen; identification of graft leaks/pseudoaneurysms
Aortic endovascular grafts	Detection of endoleaks after endovascular aortic repair (emerging)

neovascularization (Figure 14, Video 12; available at www.onlinejase.com), which may reflect plaque instability and vulnerability.[111] Although studies have shown good correlations between contrast signal intensity within plaque and subsequent histologic examination,[112,113] robust prospective studies evaluating the prognostic implications of plaque neovascularization by contrast ultrasound are needed before more routine use can be recommended.

Femoral Artery and Peripheral Arterial Disease. UEA use has been limited in femoral arteries and peripheral arterial disease (PAD). Ultrasound enhancement has been shown to be useful in cases of iatrogenic femoral artery pseudoaneurysm to delineate flow and guide percutaneous thrombin occlusion.[114] Similar to MP imaging by MCE, UEAs can also be used to assess skeletal muscle perfusion and flow reserve in the setting of chronic PAD.[115] Given the paucity of techniques to assess tissue perfusion in PAD, enhanced ultrasound is poised to become the mainstay technique to assess limb perfusion in patients.

Aortic Pathology and Grafts. Endovascular technology has progressed over the past two decades, with equivalent outcomes from endovascular aortic repair compared with open repair for many patients who require an intervention for an abdominal aortic aneurysm. Post–endovascular aortic repair surveillance includes monitoring for endoleaks, the most common complication of this procedure. Endoleaks can result in high pressure within the aneurysm sac, potentially leading to expansion and rupture. Although computed tomography (CT) remains the gold standard for endoleak detection, Doppler ultrasound has advantages, including lack of nephrotoxic contrast agents and ionizing radiation,[116] as well as the potential to noninvasively monitor in real time interventional radiologic therapeutic procedures to treat the endoleaks. UEAs are now emerging as a viable alternative to CT, whereby microbubbles detected within the residual aneurysm sac during contrast administration are indicative of an endoleak (Figure 15, Video 13; available at www.onlinejase.com). Studies have demonstrated high sensitivity and specificity for the detection of endoleaks, with contrast-enhanced ultrasound performing comparably with CT for the detection and classification of endoleaks.[116-118]

Although CT and TEE are the most common diagnostic modalities to detect type A aortic dissection, contrast enhancement of the aorta can aid in distinguishing a true intimal flap from linear artifact on both TTE and TEE. In patients with aortic dissection, contrast enhancement can also help delineate the true and false lumens (Video 14; available at www.onlinejase.com). The initial bolus of contrast needs to be imaged during the first pass to delineate the differential flow in the true and false lumens, with avoidance of attenuation from too large or too rapid an IV injection of contrast.

Key Points and Recommendations for UEA Use in Vascular Applications

1. Although the use of UEAs is off label for this purpose, there are numerous recent and developing vascular applications.
2. UEAs are recommended with low-MI ultrasound imaging of endovascular grafts to detect and classify any suspected endoleak (COR IIa, LOE B-NR).
3. Contrast ultrasound with VLMI imaging has the capability of assessing carotid artery stenosis severity and presence of plaque vascularity. Prospective studies are needed to determine the predictive value of these imaging techniques.
4. Contrast ultrasound has been used to assess limb skeletal muscle blood flow reserve in patients with diabetes and chronic PAD. Further studies are needed to determine the predictive value of this technique compared with ankle-brachial indices and CT of the peripheral vasculature.

IV.E. Contrast Echocardiography in Critical and Emergency Settings

Critical Care Settings. As detailed below, the FDA in the United States imposed a black-box warning and multiple disease-state contraindications to UEA administration in 2007, contemporaneous with the publication of the ASE consensus statement on the clinical applications of ultrasonic contrast agents in echocardiography.[1] These disease-state contraindications (acute myocardial infarction or acute coronary syndromes, worsening or decompensated heart failure, serious ventricular arrhythmias, or patients at high risk for arrhythmias on the basis of QT-interval prolongation, as well as respiratory failure, severe emphysema, pulmonary emboli, or other conditions that may cause pulmonary hypertension) essentially precluded contrast echocardiography in the vast majority of intensive care unit (ICU) patients. In one study of >58,000 hospitalized patients undergoing contrast echocardiography, 67% carried one or more of these diagnoses.[11] Although these disease-state contraindications were subsequently rescinded by the FDA, current prescribing information for each of the commercially available ultrasound contrast agents warns that the risk for serious cardiopulmonary reactions may be increased in patients with these diagnoses.[1-3] However, echocardiography is frequently technically difficult in ICU patients given patient-related factors including mechanical ventilation, wound dressings, and difficulty in patient positioning, underscoring the particular need for UEAs in this patient population. Although previous studies documented that UEAs improve image quality in ICU patients with baseline technically difficult studies, outcomes data were lacking in this patient population when the 2008 consensus statement[1] was published.

Following the FDA black-box warning in 2007, two echocardiographic outcomes studies were designed in collaboration between the FDA and UEA manufacturers. In the first of these, 2,900

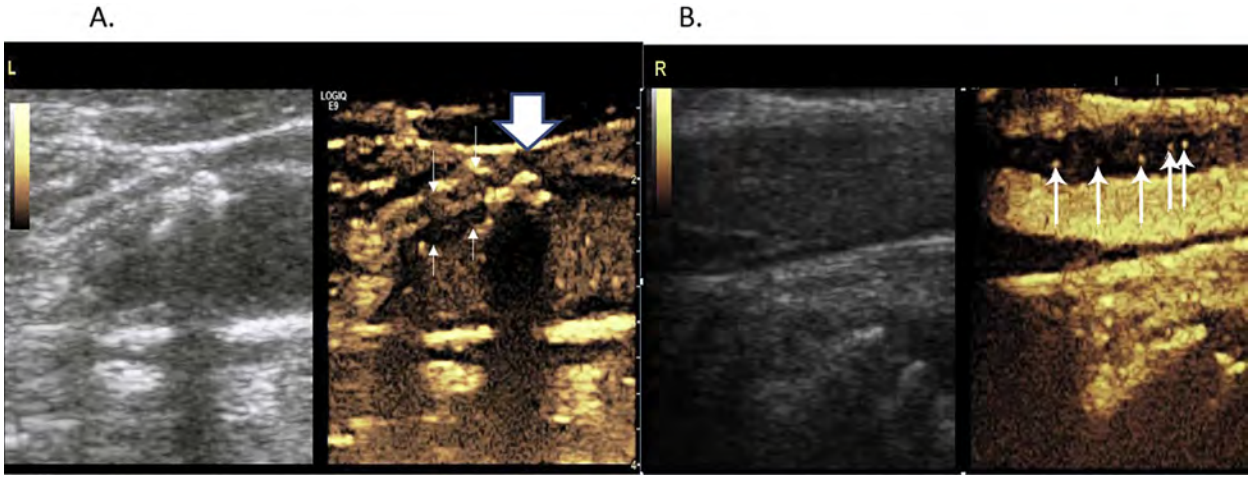

Figure 14 An example of carotid B-mode ultrasound images and contrast-enhanced low-MI harmonic images side by side in a patient with calcific carotid plaque (*large arrow*) **(A)** and minimal plaque neovascularization (*thin white arrows*). The second patient **(B)** has more extensive adventitial plaque neovascularization extending into the intima (*white arrows*). See Video 12, available at www.onlinejase.com.

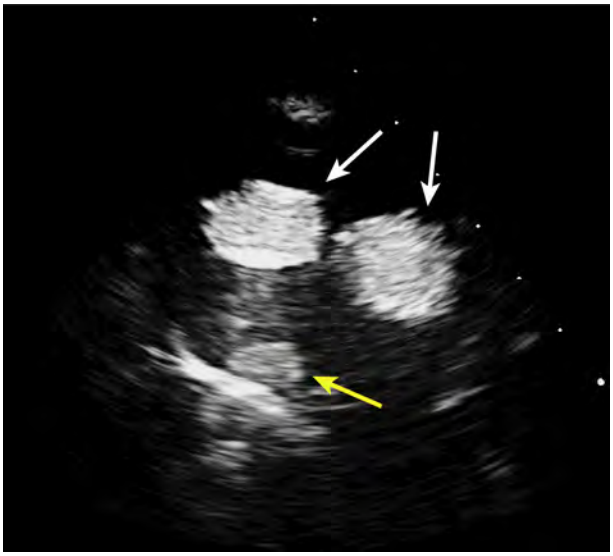

Figure 15 Short-axis view of the iliac bifurcation (*white arrows*) in a 74-year-old man status post aortic stent grafting for an abdominal aortic aneurysm. Ultrasound contrast agent–enhanced images demonstrate a type 2 endoleak (*yellow arrow*) located inferiorly and posteriorly at the graft bifurcation. The remainder of the aneurysm sac appears filled with organized thrombus. See Video 14, available at www.onlinejase.com.

critically ill patients who underwent TTE with Optison were propensity-matched with 11,600 patients undergoing unenhanced echocardiography.[18] There was no difference in short-term mortality between the two groups (odds ratio [OR], 1.18; 95% CI, 0.82–1.71; $P = .37$). In a second, larger study, 16,217 critically ill patients who underwent contrast echocardiography with Definity were propensity-matched with 16,217 patients undergoing unenhanced echocardiography.[23] At 48 hours, mortality was significantly lower in the contrast echocardiography arm (1.7% vs 2.5%; OR, 0.66; 95% CI, 0.54–0.80). Although there is no direct evidence that performance of contrast echocardiography played a causative role in this mortality difference, it is possible that earlier and more accurate diagnostic testing in these critically ill patients resulted in earlier provision of lifesaving medical therapy.

Data from a study by Kurt *et al.*[26] support this contention. A consecutive cohort of 632 patients with technically difficult echocardiographic examinations also underwent second examinations with UEAs. UEA use reduced the technically difficult study rate from 86.7% to 9.8% and resulted in conversion to a diagnostic-quality echocardiogram in virtually all of the studied patients. This resulted in a significant management change (avoidance of downstream diagnostic testing, an important medication change, or both) in 35.6% of patients. This effect was largest in patients in the surgical ICU ($n = 102$), in which UEA use resulted in significant management changes in 63% of patients. Although the benefits of UEAs in the critical care studies were primarily in improving regional and global LV systolic function analysis, additional information that can be obtained in patients with difficult windows include enhanced Doppler signals across valves for pressure gradient estimations and detection and characterization of any intracardiac masses.[1,38]

Echocardiography in the ED. Most patients presenting to the ED with chest pain do not manifest electrocardiographic ST-segment elevation, and many patients with acute myocardial infarction do not describe typical angina-quality chest discomfort. Additionally, conventional cardiac biomarker assessment has low sensitivity for detection of myocardial necrosis in the early hours of acute myocardial infarction. Given these limitations, echocardiographic assessment of wall thickening and MP (Figure 16) has been suggested as an adjunct to the traditional evaluation of patients presenting to the ED with suspected myocardial ischemia,[119] and echocardiography is endorsed for this indication in the 2011 appropriate use criteria for echocardiography.[120] Studies published before the 2008 ASE consensus statement[1] demonstrated a significant incremental diagnostic value of UEAs (assessment of both regional function and MP) in patients presenting to the ED with chest pain, as well as enhanced short-, intermediate-, and long-term prognostic value, even in the absence of cardiac biomarker data.[120] More recently, Wei *et al.*[59] studied 1,166 patients who presented to the ED with prolonged chest pain. A risk model was developed in these patients incorporating ECG, RWM by echocardiography, and echocardiographic

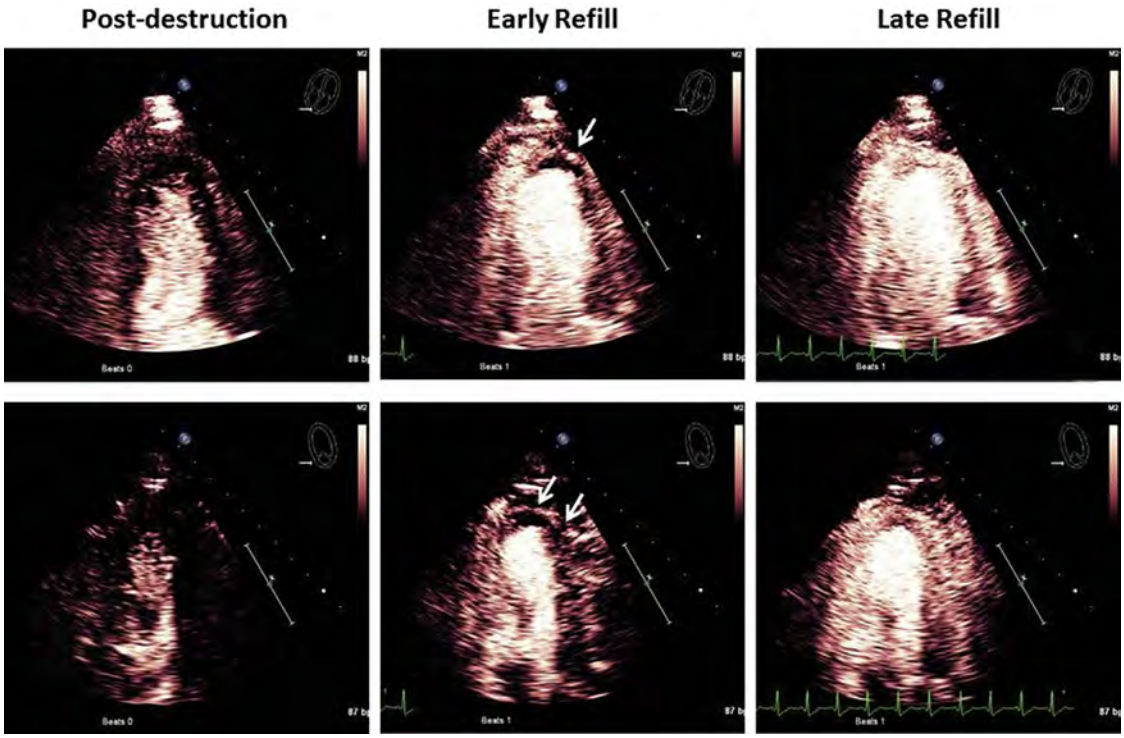

Figure 16 End-systolic frames obtained during myocardial contrast echocardiography in the apical four-chamber (*top*) and two-chamber (*bottom*) views in a patient with prior coronary bypass grafting who presented with chest pain and nondiagnostic ECG. The imaging planes were obtained immediately after high-MI impulses (*left*) and either early or late after microbubble replenishment. Early refill images illustrating delayed microbubble replenishment that is relatively less in the endocardial anterior, apical, and distal lateral regions (*arrows*). Nearly complete replenishment is seen in the late refill images (>4 sec after high-MI impulse). The bypass graft to the left anterior descending coronary artery was subsequently found to be occluded.

MP assessment and then validated in a subsequent consecutive series of 720 patients. Abnormal RWM with normal MP (OR, 3.5; 95% CI, 1.8–6.5; $P < .001$) and abnormal RWM with abnormal MP (OR, 9.6; 95% CI, 5.8–16.0; $P < .001$) were superior to electrocardiographic ST-segment abnormalities (OR, 2.9; 95% CI, 1.7–4.8; $P < .001$) in predicting nonfatal myocardial infarction or cardiac death.

Additionally, Wyrick *et al.*[60] evaluated the cost-effectiveness of MCE in 957 patients presenting to the ED with suspected myocardial ischemia and nondiagnostic ECG. Although 67% of these patients were admitted to the hospital using traditional clinical criteria (history, physical examination, ECG, and cardiac biomarkers) with an average hospitalization cost of $5,000, the authors estimated a potential $900 per patient savings with incorporation of MCE data. Five hundred twenty-three patients had normal findings on MCE and, given their subsequent very low cardiac event rate (0.6%), could have been dismissed directly from the ED, reducing the overall admission rate by 45%.

Assessment of Microvascular Obstruction Following ST-Segment Elevation Myocardial Infarction. MCE has been used to evaluate resting microvascular flow following the emergent management of ST-segment elevation myocardial infarction (STEMI).[56,121] Even following successful early recanalization of the infarct vessel, a persistent resting microvascular perfusion defect within the infarct territory has been shown to provide independent predictive value with regard to adverse LV remodeling and recurrent cardiac events (death and recurrent infarction) following STEMI. Although data are limited, it appears that VLMI imaging with UEAs permits the simultaneous assessment of two prognostically important measures before hospital discharge in post-STEMI patients: the assessment of LV systolic function and the degree of microvascular obstruction. Although angiographic recanalization with normalized epicardial flow has been achieved with contemporary percutaneous interventional techniques, microvascular obstruction may still be present in a significant percentage of patients and is prognostically important (Figure 17).

Key Points and Recommendations for UEA Use in Critical Care and Emergency Settings

1. Given a demonstrated impact on patient management and an association with mortality reduction, UEAs are recommended in all technically difficult ICU and ED patients to more quickly and accurately diagnose potentially life-threatening conditions and to reduce the need for downstream diagnostic testing. Contrast echocardiography should not be withheld on the basis of any particular diagnosis or comorbidity (COR I, LOE B-NR).
2. In patients presenting to the ED with suspected myocardial ischemia (and nondiagnostic ECG), regional function assessment with UEAs adds incremental diagnostic and prognostic value (over traditional clinical and electrocardiographic evaluation) and may reduce health care costs (COR I, LOE B-NR).
3. In patients presenting to the ED with suspected myocardial ischemia (and nondiagnostic ECG), MP assessment with UEAs adds incremental diagnostic and prognostic value (over traditional clinical, electrocardiographic, and regional function assessment) and may reduce health care costs. This technique should be considered at centers with sonographer and physician expertise in performance and interpretation of MP echocardiography (COR IIa, LOE B-NR).
4. MCE with VLMI imaging may be used in post-STEMI patients to evaluate for LV systolic function, intracavitary thrombi, and microvascular flow within the infarct territory at institutions with sonographer and physician expertise in performance and interpretation of MP echocardiography (COR IIa, LOE B-NR).

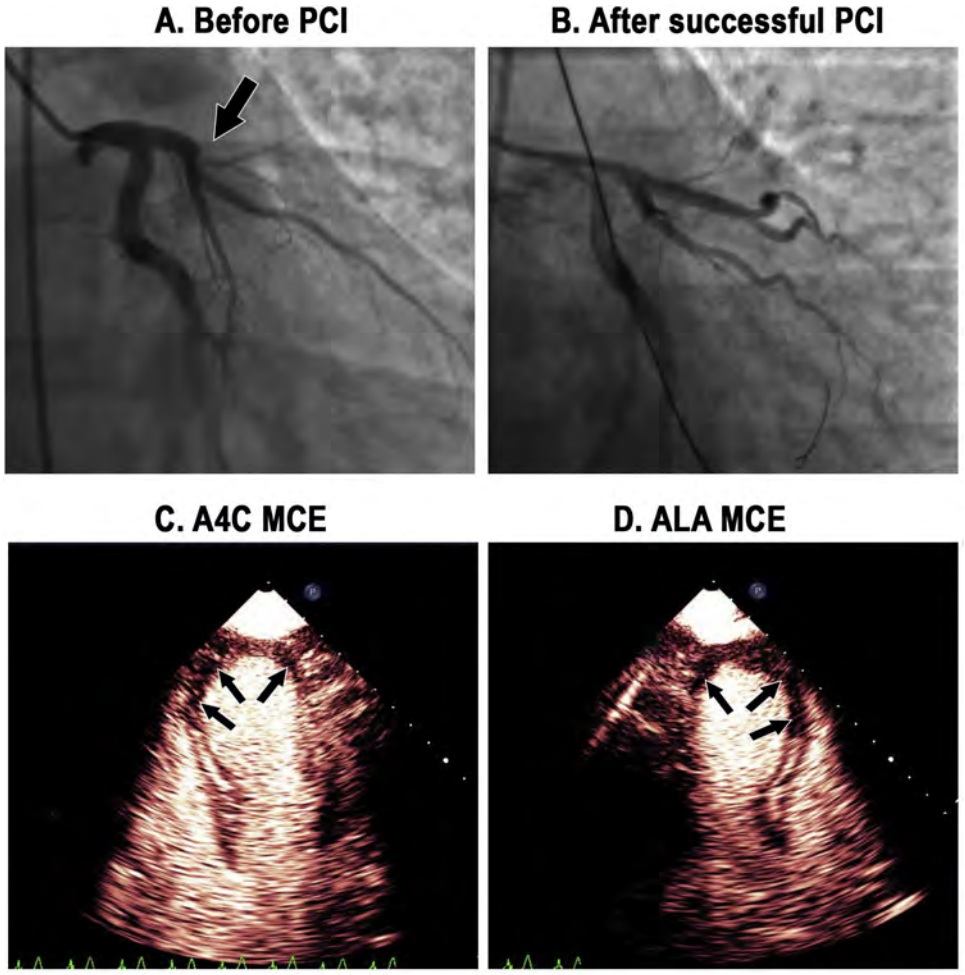

Figure 17 An example of persistent microvascular obstruction after angiographically successful percutaneous coronary angioplasty (PCI) of the left anterior descending coronary artery (LAD) **(A,B)**. During the UEA infusion 24 hours after the successful PCI, there was still a large microvascular defect in the LAD territory noted in the apical four-chamber (A4C) **(C)** and long-axis (ALA) **(D)** windows (*arrows*).

IV.F. Use of Contrast Agents in Congenital Heart Disease and Pediatric Echocardiography

Despite extensive use and proven benefits in adults, there is limited pediatric experience with UEAs. Furthermore, the FDA has not approved any of the commercially available UEAs for pediatric cardiac imaging (although Lumason is approved for pediatric liver imaging). Relatively small studies of UEAs have reported clinical benefits in children and adolescents undergoing TTE.[30,122,123] It has been shown that UEAs improve visualization of segmental wall motion in both the left and right ventricles in patients with congenital heart disease (CHD), leading to better quantification of ventricular function at rest and during physiologic or pharmacologic stress. Enhancement of Doppler signals using UEAs is beneficial for quantification of right ventricular systolic pressure in patients with CHD. As in adults, UEAs with RTMCE can provide right ventricular and LV MP information simultaneous with wall motion analysis.[30,56,122,123]

Contrary to common perception, older children can be technically challenging to image using TTE. Patients with CHD pose additional challenges due to acoustic window limitations from previous cardiac operations, chest wall issues, and alterations in cardiac geometry. UEA use both at rest and during stress echocardiography is likely to increase in the pediatric population (even for only LVO) because of increasing frequency of difficult ultrasound windows in adolescents and young adults due to prior surgical procedures and obesity, increasing number of surgical procedures involving coronary artery manipulation being performed in patients with CHD, the increasing need for evaluation of ischemia in the follow-up of acquired heart disease (e.g., Kawasaki disease), and the important need for non-radiation-exposure techniques.[30]

In patients with CHD, intracardiac communications are usually closed at the time of surgical repair, so the presence of a right-to-left shunt is rare. However, in the presence of a communication, right-to-left shunting may occur with pulmonary hypertension, right ventricular dysfunction, or diminished right ventricular compliance. It may be seen with biventricular or single ventricular CHD, but the actual site of right-to-left shunting may not be convincingly visualized, because of technical reasons. The magnitude of shunting through an intracardiac communication may also vary depending on loading conditions and streaming. Although the right-to-left shunting contraindication has recently been removed, the original intent of the FDA warning was with regard to significantly large right-to-left shunting,[38] as may be seen in some severe types of CHD. Despite removal of this warning, the Writing Group recommends further studies to document the safety of UEAs in this specific patient population. As discussed below, at the time of writing this document, there are no prospective

completed trials that have evaluated the safety of UEAs in the pediatric population. A phase 3 multicenter clinical evaluation of safety and efficacy of Lumason in pediatric echocardiography (ClinicalTrials.gov identifier NCT02282163) is currently under way. Increased clinical use in pediatrics is likely in the near future with greater experience and safety data.

It is unclear at this point what UEA use rates will eventually be for pediatrics once agents are approved, but one would expect increased use because of the increased frequency of pediatric patients surviving early surgical repairs for CHD and the increasing prevalence of obesity. The Writing Group's recommendation for training, as with adult training, would require performing 50 supervised UEA studies in the presence of a level III–trained cardiologist in echocardiography, who is experienced in UEA applications. The lower age limit in current UEA studies in pediatric populations is 5 years. There are no studies to date regarding safety in those under age 5.

Key Points and Recommendations Regarding UEA Use in Pediatric Imaging

1. The use of UEAs in children and adolescents is off label but appears safe in those 5 years and older and should be considered if Doppler signals are inadequate (see section A.1.v of the 2008 ASE consensus document) or regional LV or right ventricular wall motion analysis is not feasible with standard tissue harmonic imaging. VLMI imaging techniques should be used to optimally enhance images (COR IIa, LOE B-NR).
2. The use of UEAs is safe in pediatric and adult patients with patent foramen ovale and small right-to-left shunts. Further safety studies are needed in children and adults with large right-to-left shunts.

V. UPDATE ON SAFETY AND INDICATIONS FOR UEAs IN ADULTS

Table 1 (studies exceeding 1,000 patients) and Table 2 (smaller, focused studies) demonstrates the large body of literature that has been published since 2008.[7-10,12-17,19-24,28-34,60,123,124] These studies include UEA use in a variety of settings: inpatients, outpatients, and critically ill patients, during rest imaging and either exercise or pharmacologic stress echocardiography. Most of the studies are retrospective by design, and the majority involve the use of either Definity or Optison. The total population of subjects receiving UEAs in Table 1 exceeds 250,000 and includes patients undergoing stress echocardiography, patients in critical care settings, and patients with pulmonary hypertension. Overall, there were no reported deaths and no increases in the myocardial infarction rate or mortality in comparison with the control population. Table 2 lists smaller studies published since 2009, which evaluated UEA safety with <1,000 enrolled subjects. The safety, precautions, and benefits of UEAs in critically ill patients on mechanical circulatory support devices have been retrospectively reviewed in two single-center reports.[31,32] With regard to specific patient populations, there are no safety data published in pregnant patients or children <5 years of age.

Since 2016, all three UEA manufacturers have announced that the FDA has removed the contraindication for UEA use in patients with known or suspected right-to-left, bidirectional, or transient right-to-left cardiac shunts. Currently, Optison is contraindicated in patients with known or suspected hypersensitivity to perflutren, blood, blood products, or albumin (Table 3). Definity is contraindicated in patients with known or suspected hypersensitivity to perflutren (Table 3).

In October 2014, a third UEA, Lumason, was approved by the FDA for use in adults with suboptimal echocardiograms to opacify the LV chamber and to improve the delineation of the LV endocardial border.[4] In March 2016, Bracco Diagnostics also announced that the FDA had approved Lumason for use in ultrasonography of the liver for characterization of focal liver lesions in both adult and pediatric patients. Although restricted to liver imaging, this action made Lumason the first ultrasound contrast agent the FDA approved for use in the pediatric population. Lumason also gained FDA approval for use in the evaluation of suspected or known vesicoureteral reflux in pediatric patients. Safety was based on evaluation of published literature involving use of Lumason in >900 pediatric patients. Nonfatal anaphylaxis was reported in one pediatric patient.[3] Currently, Lumason is contraindicated in patients with histories of hypersensitivity reactions to sulfur hexafluoride lipid microsphere components or to any of the inactive ingredients in Lumason.

These recent FDA changes follow other safety label alterations that were made from 2008 to 2011 for both Optison and Definity, as described in the 2014 ASE contrast sonographer guidelines update.[38] All studies have demonstrated that life-threatening reactions with UEAs are extremely rare, approximately one in 10,000. It is advised by the ASE, and mandated by the Intersocietal Accreditation Commission,[5] that a policy be in place for early identification and rapid response to these acute and severe reactions. All personnel, including sonographers, registered nurses, exercise physiologists, and physicians, should be familiar with the early identification of an allergic reaction and the appropriate treatment. The ASE and the Intersocietal Accreditation Commission recommend that a policy be in place before the use of any contrast agent and that personnel be well trained in its implementation. Allergy kits should be available and easily accessible in all areas where UEAs are in use and should be frequently logged for expiration dates. Auto-injectable epinephrine (available as EpiPen; Mylan Specialty, Basking Ridge, NJ) is the most important component of these kits and can be lifesaving in the case of anaphylactic shock. Most contrast-related reactions occur immediately or within the first 30 min after UEA use. Anaphylactoid reactions, presumed to be a type I hypersensitivity reaction known as complement activation–related pseudoallergy, and characterized by skin erythema, urticaria, rash, dyspnea, throat tightness, flushing, and difficulty swallowing and/or anaphylactic shock, have been reported at a very low incidence, with serious reactions reported at less than one in 10,000.[1] A low incidence of temporary back pain seems to be linked to Definity and usually resolves spontaneously within a short period without treatment,[1] the causes of which are not entirely understood but may be related to retention of lipid microbubbles within glomerular capillaries. This retention is significantly less with albumin microbubbles such as Optison.[24]

Recommendations Regarding the Safety of UEAs

1. Abundant literature (see Tables 1 and 2) exists supporting the safety of UEA use in nonpregnant adults. These are supported by FDA modifications in the black-box warning since the 2008 ASE contrast consensus statement (Table 6).
2. Although anaphylactoid reactions are rare, laboratories that routinely use UEAs should have policies in place for emergent resuscitation of patients who may experience serious side effects.
3. UEAs can safely be used in patients with pulmonary hypertension and with right-to-left shunts (COR I, LOE B-NR).
4. No safety data exist for the use of UEAs in pregnancy or children <5 years of age. UEA use is therefore not recommended in these groups until safety data emerge.

Table 6 FDA product label changes, 2007 to 2017

Year	Change	Notes
2007	FDA issues black-box warning	Although actual causality was never proved, because of the deaths of a few patients with a temporal association with UCA use, the FDA issued a black-box warning and added a new contraindication for patients with PH and unstable CPD and required the monitoring of all patients for 30 min after UCA use.
2008	Black-box warning lessened limitations for monitoring	After review of a series of publications from the ultrasound community confirming the safety of UCAs, the FDA modified the "contraindication" of use in PH and unstable CPD to warnings and limited the monitoring to only those patients with PH and unstable CVD. References: postmarketing safety studies released: Kusnetzky *et al.*,[10] Main *et al.*,[11] and Wei *et al.*[24]
2011	Definity, black-box warning removal of monitoring, stress testing	Definity label changes after FDA review of data from the risk modifications studies included removal of the requirement for monitoring of patients with PH and unstable CPD after use of Definity, and the statement regarding the efficacy and safety of Definity had not been established in stress testing. References: Abdelmoneim *et al.*[17] (PH safety), Gabriel *et al.*,[8] Shaikh *et al.*,[12] and Dolan *et al.*[16] (stress testing safety)
2012	Optison, black-box warning removal of monitoring, stress testing	Optison label changes similar to Definity (2011). FDA removes the need for monitoring of patients with PH and unstable CPD and the statement regarding the efficacy and safety of Optison not established in stress testing. References: Abdelmoneim *et al.*,[17] Wever Pinzon *et al.*[21] in PH
2014	FDA approval of Lumason for use in the United States	October 2014: Lumason is approved by the FDA for cardiac use in adults for LVO and endocardial border detection.
2016–2017	Black-box warning removal of shunts as contraindication	March 2016: Lumason receives FDA approval for use in ultrasonography of liver lesions in both adult and pediatric patients. October 2016: Optison label change removing shunt contraindication and use in intra-arterial injection to warnings only. December 2016: Lumason label removal of the contraindication for cardiac shunts. Addition of FDA approval for use in the evaluation of vesicoureteral reflux in pediatric patients. Definity label change to removal of the contraindication for use in patients with known or suspected right-to-left, bidirectional, or transient right-to-left cardiac shunts to warning. References: Kalra *et al.*[33] and Parker *et al.*[124] (safety in use with shunts)

CPD, Cardiopulmonary disease; *CVD*, cardiovascular disease; *PH*, pulmonary hypertension; *UCA*, ultrasound contrast agent.

VI. ECHOCARDIOGRAPHY LABORATORY IMPLEMENTATION OF CONTRAST AGENT USE

Physicians

Current training standards for echocardiography are described in detail in the COCATS 5 Task Force 4 document, published in 2015.[125] Physicians who wish to acquire skills for perfusion imaging should obtain additional training at a high-volume center with special expertise in the assessment of MP.[1,38,126] Standards for advanced echocardiographic training are currently being written and will be published in the near future.

Physicians trained in focused ultrasound are often confronted with difficult cardiac windows when making bedside assessments of RWM and ejection fraction. Specific training on the use of UEA and interpretation of these echocardiograms by physicians is needed. Recommendations and standards on such training will be the scope of future multisociety documents.

Sonographers

Previously published 2014 ASE guidelines for cardiac sonographers in the performance of contrast echocardiography support sonographer training in IV insertions for the purpose of UEA administration in hospitals and clinic settings, to improve echocardiographic quality with increased efficiency.[38] Personnel qualified to start an IV line and administer contrast will vary by center according to local hospital policies. At the majority of centers in North America, the IV start and contrast administration will be performed by a registered nurse, medicine technician or phlebotomist, or fellow in training, whereas some sites have extended this responsibility to sonographers.[38] The training of sonographers in IV line insertion and contrast administration requires hospital approval, knowledge of sterile technique and venous anatomy, and awareness of associated risks. Although serious side effects are exceedingly rare, there should always be a physician present on site when contrast is administered. Two single-center studies in Europe and Canada have demonstrated improved efficiency with sonographer-driven contrast echocardiographic protocols through reductions in time to decision for contrast use and time to administration of contrast, resulting in potential cost savings.[127,128] This also underscores that training in the recognition of need for UEA must be a standard component of sonographer education, complemented by echocardiography laboratory implementation of standing orders for UEA administration.

Recommendations

1. Physicians wishing to perform contrast echocardiography independently should receive supervised training and interpretations by a level III–trained person. Perfusion imaging training requires specific training and performance and interpretation of additional rest and stress perfusion studies (COR I, LOE C-EO).
2. Sonographers should be trained in the establishment of IV lines and contrast administration, to improve operational efficiency in the echocardiography laboratory. It is recommended that this skill be included in the sonography school curriculum (COR I, LOE C-EO).

Table 7 Emerging applications of UEAs

	Microbubbles required	Ultrasound instrumentation required	Specific applications
Thrombolysis	Commercially available/targeted	Intermittent diagnostic high-MI impulses	Acute coronary syndromes, ischemic stroke
Molecular imaging	Targeted/phosphatidyl serine–bearing commercial microbubbles*	High-MI imaging after blood pool clearance	Ischemic memory imaging Plaque inflammation Early plaque formation Myocarditis/transplant rejection
Targeted drug/gene delivery	Commercially available/targeted	Intermittent diagnostic high-MI impulses following bolus injection	DNA/RNA delivery for atherosclerosis, limb ischemia, myocardial regeneration, antiangiogenesis in targeted tumor therapy
Diagnostic ultrasound–induced inertial cavitation	Commercially available	Intermittent diagnostic high-MI impulses	Improved downstream skeletal muscle perfusion in ischemic limbs (sickle-cell disease) Improved microvascular outcome in acute coronary syndromes

DNA, Deoxyribonucleic acid; *RNA*, ribonucleic acid.
*Sonazoid is the only commercially available microbubble with phosphatidyl serine on the shell.

VII. EMERGING APPLICATIONS

Emerging applications are detailed in Table 7.

VII.A. Sonothrombolysis

The potential for intermittent high-MI impulses from a diagnostic transducer to dissolve intravascular thrombi was first demonstrated in a canine model of arteriovenous graft thrombosis, in which intermittent high-MI impulses (all <1.9) were applied when low-MI imaging detected microbubbles within the graft.[129] The high-MI impulses were shown to induce inertial cavitation within the graft, resulting in fluid jets, which have been shown to mechanically erode thrombus.[130] Recanalization with the guided high-MI impulses was achieved without any adjunctive fibrinolytic, antithrombotic, or antiplatelet agents, suggesting that the cavitation and radiation effects of high-MI impulses observed in in vitro studies were sufficient to dissolve thrombi. This study prompted subsequent investigations that examined the efficacy of diagnostic high-MI impulses in restoring microvascular and epicardial blood flow in porcine models of acute STEMI.[131,132] Because epicardial vessels are not easily visualized with diagnostic ultrasound (DUS), these studies used VLMI imaging of the microvasculature to guide the timing of the high-MI impulses. Even with transthoracic attenuation, these studies demonstrated that intermittent high-MI impulses from a DUS transducer could increase the epicardial recanalization rates from 36% seen with a half dose of tissue plasminogen activator alone to 83% with DUS high-MI impulses and microbubbles combined with a half dose of tissue plasminogen activator. Also, ST-segment resolution (indicating microvascular recanalization) was seen with DUS high-MI impulses even when epicardial recanalization was not observed, indicating that vasoactive mediators were playing a role in restoring microvascular flow, in addition to epicardial thrombus dissolution. Subsequent studies in ischemic peripheral vessel occlusion have confirmed that high-MI DUS impulses can induce nitric oxide release, resulting in restoration of microvascular flow, even in the presence of an upstream vessel occlusion.[133] Preliminary clinical studies in patients with acute STEMI have demonstrated that the guided high-MI diagnostic impulses (3-μsec pulse duration) are sufficient to improve early epicardial recanalization rates and restore microvascular flow (Figure 18) with commercially available IV microbubbles.[134] Ongoing studies will examine the safety and efficacy of this DUS targeted sonothrombolytic technique in acute coronary syndromes as well as in ischemic stroke.

VII.B. Molecular Imaging

Although UEAs are composed of microbubbles that act as free intravascular tracers, ligands can be attached to their surface that cause them to attach to dysfunctional endothelium. These can be imaged with contrast-specific imaging protocols for both diagnostic and therapeutic purposes. A common approach is to pair a novel site-targeted imaging probe with conventional approaches to noninvasive contrast imaging.[135] Although clinical translation has been slow, molecular imaging has the potential to improve outcomes or efficiency of care through early diagnosis of disease and guided selection of therapy. Molecular imaging has also been used in preclinical research to assess on-target and off-target effects of new therapies and to identify new pathways for intervention.

Molecular imaging with targeted contrast ultrasound relies on the selective retention at sites of disease of any one of several different types of acoustically active targeted imaging molecules, ranging in size from a few hundred nanometers to several micrometers. The use of microbubbles that have undergone modification of their shell has been the most common approach on the basis of the relative simplicity of agent preparation, the high degree of signal generation provided during conventional contrast imaging, and the rapid clearance from the circulation after IV injection. The latter issue is important because discrimination of signal from retained agent is usually accomplished by imaging after time is allowed for clearance of the freely circulating nonattached population of microbubbles. Because most acoustically active contrast agents are confined to the vascular compartment, UEAs have been targeted primarily to

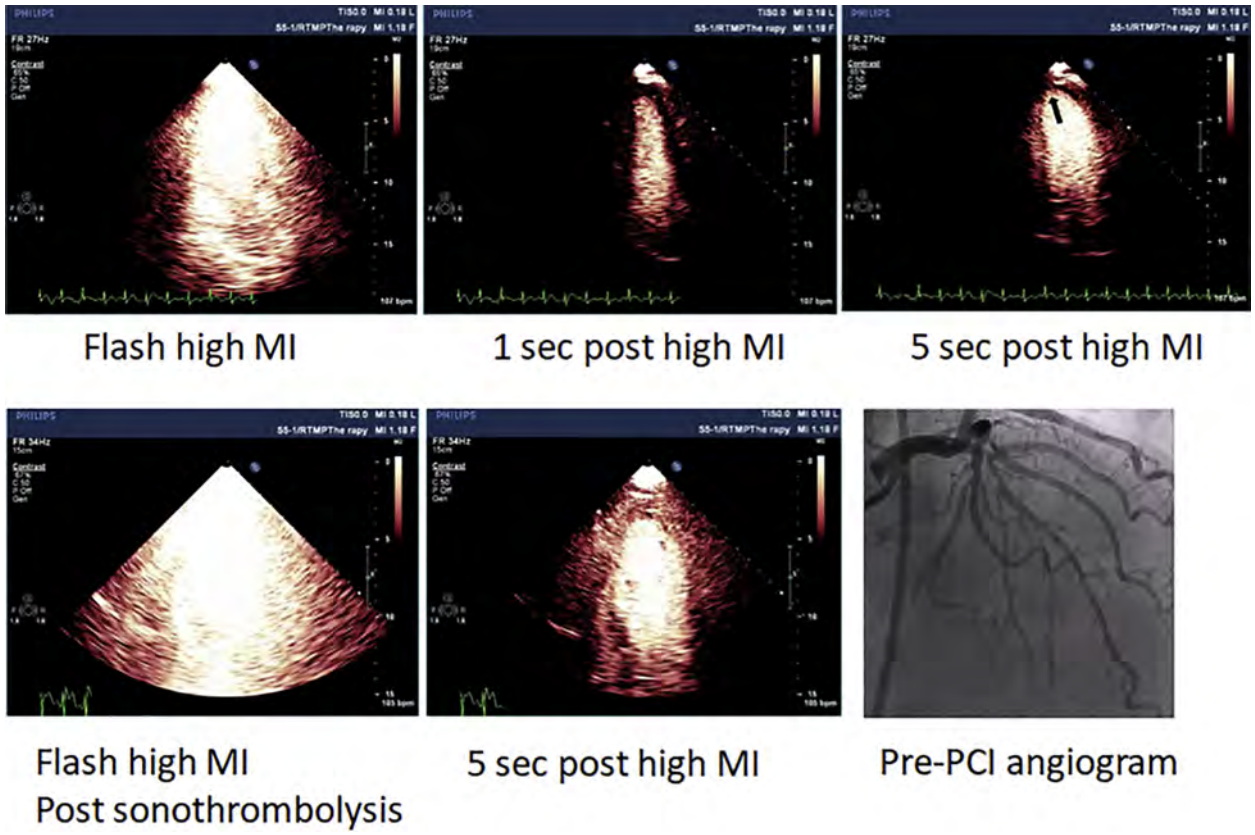

Figure 18 A patient with an anterior STEMI treated with repeated high-MI diagnostic impulses during a dilute UEA infusion before percutaneous coronary intervention (PCI). The *top row* depicts apical microvascular obstruction (*arrow*) in the apical two-chamber view on the initial images obtained as the patient arrived to the ED. A brief (10- to 20-min) period of intermittent high-MI impulses was applied in each apical view during UEA infusion before reaching the cardiac catheterization laboratory, resulting in resolution of the apical defect (*lower row*, *middle panel*) and angiographic recanalization on the initial projections obtained before stent placement in the left anterior descending coronary artery (*bottom row*, *right panel*).

events that occur within the blood pool or at the blood pool–endothelium interface.[136]

One of two strategies has accomplished targeting of ultrasound agents. A simple approach has been to select certain microbubble shell constituents that facilitate their attachment to either leukocytes or activated endothelium in regions of disease. Lipid-shelled microbubbles bearing phosphatidylserine have been shown to be particularly effective in this regard and have recently been shown to provide a simple approach for noninvasive detection of recent myocardial ischemia.[137] At the time of this publication, none of these agents is available in the United States or Europe. Sonazoid (a phosphatidylserine-bearing microbubble) is available for noncardiac imaging in Japan.

More specific targeting is achieved by conjugating ligands (generally at the end of a molecular spacer arm) to the microbubble surface in densities of up to several thousand per square micrometer of surface area. The combination of ligand/target density and bond kinetics must be sufficient to withstand vascular shear forces.[138] Microbubbles targeted to endothelial adhesion molecules and other activated endothelial markers (vascular cell adhesion molecule–1, intercellular adhesion molecule–1, selectins, integrins) have been used to detect preatherogenic potential or plaque inflammatory phenotype.[139-143] Some of these agents have also been used to image myocardial ischemia, transplant rejection, myocarditis, and angiogenesis.[144-151] Microbubbles targeted to fibrin, platelet components of the coagulation system (glycoprotein IIb/IIIa, glycoprotein Ib), and von Willebrand factor have been used to identify either cavitary or arterial thrombus, microthrombi, or plaque prothrombotic and proinflammatory potential.[141,152,153] Microbubbles targeted to specific subsets of monocytes have also been used for imaging of ischemia-related vascular remodeling.[148] Targeted microbubbles have also been used in preclinical research for augmentation of ultrasound-based therapies such as targeted delivery of stem cells or genes (plasmid complementary deoxyribonucleic acid) or enhancement of sonothrombolysis.[154-156]

VII.C. Targeted Drug and Gene Delivery

Targeted gene and drug delivery can be facilitated noninvasively by the ultrasonic destruction of intravenously administered carrier microbubble UEAs, most frequently termed ultrasound-targeted microbubble destruction (UTMD). Although ultrasound energy alone can facilitate gene transfection by sonoporation (cavitation-induced transient pore formation or altered permeability) and by active cell

Table 8 Comparison of information obtained from a real-time myocardial contrast echocardiographic stress study and a stress single-photon emission computed tomographic study

Procedure	Resolution	Prognostic data?	Stress EF?	Rest EF	Diastolic function	Costs*	Radiation exposure
Stress RTMCE	3 mm	Yes	Yes	Yes	Yes	$309.36	0
Stress SPECT	10 mm	Yes	No	Yes	No	$1,600.74	15.6 mSv[187]

EF, Ejection fraction.
*Global and technical Medicare reimbursement information using CPT code 78452 for single-photon emission computed tomographic multiple myocardial perfusion and CPT codes 93351 and 93352 for stress TTE with exercise and use of contrast at stress.

uptake, the addition of microbubbles lowers the threshold for acoustic cavitation and markedly increases transfection efficiency, particularly when genes or nucleic acids are incorporated or charge-coupled directly to the microbubble surface.[156-159] Delivery and transfection occur by several mechanisms, including transient pore formation and active calcium-mediated cell uptake, both of which are likely a result of cavitation-related shear forces, microjets, shock waves, and pressure-related cell deformation.[160,161]

UTMD delivery can be optimized by the use of triggered DUS to allow replenishment of the tissue with carrier microbubbles between destructive pulses and creating an ideal acoustic environment for inertial cavitation (high acoustic power or MI, lower transmit frequency).[162] As carrier microbubbles are purely intravascular, transfection and delivery occur predominantly to the vascular endothelium of the insonified tissue but can produce extravascular transfection and delivery as well. From a safety perspective, studies have shown that high levels of transfection can occur at acoustic pressures just less than those that produce adverse bioeffects[156] and that minimal to no remote transfection occurs outside the area insonified by the ultrasound beam,[163-165] demonstrating the targeted nature of delivery by UTMD. Furthermore, many of these preclinical studies have used the diagnostic high-MI impulses available on commercially available transducers to achieve UTMD and targeted drug delivery.

Although the initial in vivo study of UTMD for gene delivery used recombinant adenovirus,[166] the vast majority of subsequent studies have used plasmid deoxyribonucleic acid, with more recent studies using other nucleic acids such as small interfering ribonucleic acid[167] and micro–ribonucleic acid.[168] To date, studies of UTMD for therapeutic applications have been confined to preclinical studies in a wide variety of animal models of disease, including cardiovascular, cancer, hepatic, renal, and cerebral diseases. Within cardiovascular diseases, UTMD of many different therapeutic genes has been applied successfully to models of acute myocardial infarction,[169] chronic myocardial infarction and ischemic cardiomyopathy,[170] dilated cardiomyopathy,[171-173] and PAD,[174] as well as to animal models of type 1 diabetes to restore endocrine pancreatic function.[175] Given the modest transfection efficiency, the beneficial effects of UTMD are most prominent when either transfecting a paracrine factor or transfecting a gene that has a significant effect even when the majority of cells are not transfected.[171,176] A comprehensive review of UTMD for gene and drug delivery for cardiovascular applications is beyond the scope of this document. However, several excellent reviews have been published within the past few years.[177,178] Although UTMD has potential advantages over other gene delivery techniques, including its noninvasive nature that allows multigene therapy,[169,170] ongoing work is focusing on improving transfection efficiency using newer vectors that prolong transfection or promote chromosomal insertion.

VII.D. Flow Augmentation with Diagnostic UTMD

As stated above, diagnostic high-MI impulses induce inertial cavitation of UEAs in vivo. In addition to the thrombolytic effects, this cavitation process has augmented tissue blood flow via mechanisms that are mediated by nitric oxide production.[133] Recent preclinical data have demonstrated that diagnostic UTMD produces a 40-fold increase in adenosine triphosphate release that is sustained for several minutes after ultrasound exposure.[179] The vasculature that is fed by the vessels being insonified (downstream vessels) experienced increases in tissue blood flow in this animal model, and increased adenosine triphosphate release was observed for up to 24 hours after diagnostic UTMD. The therapeutic potential for this has been demonstrated in patients with sickle-cell anemia, in whom intermittent high-MI DUS impulses during a commercially available IV UEA infusion resulted in improved skeletal muscle perfusion.[179]

VIII. COST-EFFECTIVENESS OF UEAS

In the United States, hospitals are reimbursed for the provision of inpatient care by the Centers for Medicare and Medicaid Services (and most private commercial payers) under diagnosis-related groups. Under this system, a particular diagnosis or clinical condition is associated with an essentially flat reimbursement for the hospital stay; therefore, hospitals are incentivized to provide the most efficient care. With respect to UEAs, cost-effectiveness can be examined in specific contexts, as outlined below.

Reducing Costs per Patient

Echocardiography is a highly efficient diagnostic test, given relatively low imaging platform costs (in comparison with radionuclide tracer imaging, CT, CMRI, and cardiac catheterization), low staffing requirements (one sonographer per examination), low supply costs, potential for portable examinations, excellent reproducibility, and high throughput. UEA use is reimbursed by Medicare and third-party payers in the hospital outpatient department setting (C8929, "TTE rest echo complete with contrast"; and C8930, "stress TTE with contrast and ECG monitoring"). As of 2017, these are reimbursed approximately $200 more than the same studies without contrast. In hospitalized patients with technically difficult echocardiographic examinations, the use of UEAs may increase this cost efficiency, even though the agents are not separately reimbursed. In a study of 632 patients with technically difficult echocardiographic examinations, each of whom also underwent a second contrast-enhanced examination,[26] UEAs reduced the technically difficult study rate from 87% to 10% and resulted in a significant management change (avoidance of downstream diagnostic testing, an important medication change, or both) in 36% of patients.

In the overall cohort, the cost of contrast was $39,184, and the total cost of avoided procedures (TEE and nuclear cardiology) was $116,094, for a total savings of $76,910, or $122 per patient. Of note, the impact on patient management was greater in inpatients than outpatients, and the cost savings in the inpatient arena were likely significantly higher than was reported for the overall cohort.

Improving Positive Predictive Value

The cost-efficiency of a diagnostic technique is based on initial cost, the frequency of the diagnostic result obtained, and the accuracy of the test for the diagnosis and prognosis of the condition. Lack of diagnostic results gives rise to more downstream tests, which increase the cost of the particular strategy. It was clearly shown in the previous section that when UEAs are used for LVO, diagnostic test frequency is decreased, leading to reduced downstream cost. Improved accuracy leads to more appropriate referral for coronary angiography, with negative tests showing minimal rates of hard events and revascularization. It has also been shown that adding perfusion assessment to wall motion assessment during stress echocardiography further improves accuracy, for both diagnosis and prognosis of CAD. In a recent study, perfusion assessment improved the positive predictive value for CAD detection from 83% to 90% compared with wall motion and improved outcome assessment.[60] In a large randomized study comparing RTMCE for perfusion and function versus non-MCE contrast echocardiography for wall motion only, more flow-limiting CAD was identified by a perfusion technique, which may translate into improved outcomes.[45] Although no formal cost analysis was carried out, on the basis of improved accuracy of diagnosis and prognosis compared with wall motion, perfusion is likely to be cost saving, although the magnitude of initial cost of LVO stress echocardiography versus perfusion stress echocardiography is important in this equation. More recent studies in preoperative risk assessment before major surgery (kidney and liver transplantation) have demonstrated the incremental value of perfusion combined with wall motion imaging during DSE in predicting adverse cardiovascular outcomes.[180,181]

Improving the Emergent Evaluation of a Patient

The concept that MP imaging can improve cost-effectiveness in patients presenting to the ED with chest pain was first established using single-photon emission computed tomographic radionuclide imaging.[182] Cost-effectiveness in this setting is based on both the ability to exclude patients who have cardiac causes of their chest pain and rapid identification of those who are likely to benefit from therapy for acute coronary syndrome.[183] MCE represents a more practical approach to perfusion imaging in ED patients because it is able to be performed rapidly at the bedside, it is less expensive than SPECT, and it provides immediate information to the clinician. When performed in the ED, MCE for both wall motion and perfusion has been shown to provide incremental benefit to standard clinical data in terms of stratifying patient risk.[184] Accordingly, MCE has been predicted to save approximately $900 per patient in those admitted to the ED, largely because of the prevention of unnecessary hospital admissions and additional cardiovascular testing.[60]

In the critical care setting, limited data exist with regard to the impact of UEAs. In the serial echocardiographic evaluation of LV assist device therapy, in which image quality is frequently poor, emerging evidence suggests that UEA use alters patient management in >40% of cases, including adjustments in pump speed and detection of pump thrombosis.[31]

Key Points and Recommendations

1. The use of UEAs is recommended in all difficult-to-image hospitalized patients (COR I, LOE B-NR). Although separate reimbursement for UEAs is not provided in the inpatient setting, overall cost savings are realized because of avoidance of downstream diagnostic testing, including TEE and nuclear cardiac testing. Additional cost-effectiveness studies are warranted, including evaluation of contrast echocardiography on hospital length of stay.
2. When echocardiography laboratories are adequately trained in perfusion imaging, MCE should be used for both stress echocardiography (COR IIa, LOE B-R) and in the ED evaluation of patients with chest pain and nondiagnostic ECG to evaluate both MP and RWM (COR IIa, LOE B-NR).
3. Additional clinical studies are needed to evaluate the impact of UEAs in the critical care setting.

IX. SUMMARY OF RECOMMENDATIONS FOR UEA USE FOR ECHOCARDIOGRAPHY AND ADDITIONAL RESOURCES

Since the 2008 ASE consensus statement,[1] there have been significant clinical developments, including additional documentation regarding the safety and efficacy of UEA use for improving LVO in several clinical settings. This has been accompanied by the removal and/or reductions of prior contraindications to use and the provision of new clinical data to support use in pediatrics as well as nonapproved indications such as MP imaging and therapeutic thrombolysis. Indeed, the data regarding perfusion imaging is so compelling that European guidelines have recommended UEAs as a method of evaluating patients with stable chest pain.[185] A recent meta-analysis demonstrated that abnormal perfusion by MCE during exercise, dobutamine, or vasodilator stress imaging has a fivefold greater risk for cardiac events compared with normal perfusion, with low heterogeneity among trials.[186] Table 8 compares the information obtained, costs, and risks that are part of stress MCE and perfusion stress SPECT in a hypothetical American Medicare patient.

In the United States, a unique add-on billing code has been established for MP using UEAs (CPT code +0439T), and the Writing Group recommends that this code be used in laboratories that are experienced in UEA use, especially during rest studies to evaluate chest pain or shortness of breath, as well as during stress echocardiography or viability testing. In those laboratories without adequate experience with UEAs for the indication of LVO, it is recommended that experience be acquired to provide state-of-the-art contrast echocardiography and comply with national accreditation standards. Also, ultrasound vendors of both large and small systems must work in unison to provide front-end presets that will enable users to more readily access the imaging presets and functionality that are optimized for LVO and perfusion.

Additional educational material in the areas of microbubble physics, UEA administration protocols and policies, and techniques and tips for LVO and MP imaging can be found at http://www.asecho.org/contrast. Further updates are expected as additional clinical studies emerge in the areas of cost-effectiveness of UEA use, perfusion imaging, sonothrombolysis, molecular imaging, and targeted drug and gene delivery. The Writing Group emphasizes the critical need for vendors to improve their VLMI imaging protocols and presets on their existing systems, including their portable systems, as more physicians in cardiology, critical care, and emergency care use UEAs to improve diagnostic capabilities.

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SUPPLEMENTARY DATA

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