American Society of Echocardiography Consensus Statement on the Clinical Applications of Ultrasonic Contrast Agents in Echocardiography

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Continuing Medical Education Course for "American Society of Echocardiography Consensus Statement on the Clinical Applications of Ultrasonic Contrast Agents in Echocardiography"

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The ASE designates this educational activity for a maximum of 1 *AMA PRA Category 1 Credit*.™ Physicians should only claim credit commensurate with the extent of their participation in the activity.

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Target Audience:

This activity is designed for all cardiovascular physicians, cardiac sonographers, and nurses with a primary interest and knowledge base in the field of echocardiography; in addition, residents, researchers, clinicians, sonographers, and other medical professionals having a specific interest in contrast echocardiography may be included.

Objectives:

Upon completing this activity, participants will be able to: 1. Demonstrate an increased knowledge of the applications for contrast echocardiography and their impact on cardiac diagnosis. 2. Differentiate the available ultrasound contrast agents and ultrasound equipment imaging features to optimize their use. 3. Recognize the indications, benefits, and safety of ultrasound contrast agents, acknowledging the recent labeling changes by the US Food and Drug Administration (FDA) regarding contrast agent use and safety information. 4. Identify specific patient populations that represent potential candidates for the use of contrast agents, to enable cost-effective clinical diagnosis. 5. Incorporate effective teamwork strategies for the implementation of contrast agents in the echocardiography laboratory and establish guidelines for contrast use. 6. Use contrast enhancement for endocardial border delineation and left ventricular opacification in rest and stress echocardiography and unique patient care environments in which echocardiographic image acquisition is frequently challenging, including intensive care units (ICUs) and emergency departments. 7. Effectively use contrast echocardiography for the diagnosis of intracardiac and extracardiac abnormalities, including the identification of complications of acute myocardial infarction. 8. Assess the common pitfalls in contrast imaging and use stepwise, guideline-based contrast equipment setup and contrast agent administration techniques to optimize image acquisition.

Author Disclosures:

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  - Ventricular noncompaction
  - Apical thrombus
  - Complications of myocardial infarction, such as LV aneurysm, pseudoaneurysm, and myocardial rupture
- To assist in the detection and correct classification of intracardiac masses, including tumors and thrombi

Table 1 Echocardiographic contrast agents

Agent	Bubble size (μm), mean (range)	Gas	Shell composition	Indication
Levovist*,†	2.0-3.0 (2.0-8.0)	Air	Lipid (palmitic acid)	LVO and Doppler
Optison‡,§	4.7 (1.0-10.0)	Perfluoropropane	Human albumin	LVO, EBD, and Doppler
Definity‡,‖	1.5 (1.0-10.0)	Perfluoropropane	Phospholipid	LVO, EBD, and Doppler
SonoVue*,#	2.5 (1.0-10.0)	Sulfur hexafluoride	Phospholipid	LVO and Doppler
CARDIOsphere**,††	4.0 (3.0-5.0)	Nitrogen	Biodegradable polymer bilayer	MCE
Imagify**,‡‡	2.0	Decafluorobutane	Synthetic polymer	LVO and MCE

LVO, Left ventricular opacification; EBD, endocardial border definition; MCE, myocardial contrast echocardiography (perfusion).
*Approved in Canada, Europe, and some Latin American and Asian countries.
†Bayer Schering Pharma AG (Berlin, Germany).
‡Approved by the FDA. Optison and Definity are also approved in Canada, and Definity is approved in Europe under the name Luminity.
§GE Healthcare (Princeton, NJ).
‖Lantheus Medical Imaging (North Billerica, MA).
#Bracco Diagnostics (Milan, Italy).
**Not yet FDA approved.
††POINT Biomedical Corporation (San Carlos, CA).
‡‡Acusphere (Watertown, MA).

- For echocardiographic imaging in the intensive care unit (ICU) when standard tissue harmonic imaging does not provide adequate cardiac structural definition
  - For accurate assessment of LV volumes and LVEF
  - For exclusion of complications of myocardial infarction, such as LV aneurysm, pseudoaneurysm, and myocardial rupture
- To enhance Doppler signals when a clearly defined spectral profile is not visible and is necessary to the evaluation of diastolic and/or valvular function

PURPOSE

Ultrasound contrast agents, used with contrast-specific imaging techniques, have an established role for diagnostic cardiovascular imaging in the echocardiography laboratory. This document focuses on when and how contrast agents are used to enhance the diagnostic capability of echocardiography. It also reviews the role of physicians, sonographers, and nurses, as well as ways to integrate the use of contrast agents into the echocardiography laboratory most efficiently. These recommendations are based on a critical review of the existing medical literature, including prospective clinical trials. Where no significant study data are available, recommendations are based on expert consensus opinion. Updating a previous publication,[1] this document describes the evidence-based use of contrast echocardiography in clinical practice while acknowledging recent labeling changes by the US Food and Drug Administration (FDA) regarding contrast agent use and safety information, as described in section B.

INTRODUCTION

Radiographic and paramagnetic contrast agents have an important role in current noninvasive imaging techniques. They are essential for delineating vascular structures with computed tomography (CP) and for perfusion and viability studies with magnetic resonance imaging, and they are an integral part of all nuclear cardiac imaging techniques. Historically, contrast agents have not been an integral component of the echocardiography imaging laboratory. However, a unique class of contrast agents composed of microbubbles, rather than dyes, chemical compounds, or radioisotopes, has been developed, along with new ultrasound imaging techniques that optimize their detection.

CONTRAST AGENTS

Ultrasound contrast agents have an established role in clinical diagnosis, patient management, and clinical research. The contrast agents that are approved by regulatory agencies for echocardiographic use throughout the world (Table 1) share the common indications, as approved by the FDA, of LV opacification (LVO) and LV endocardial border definition (EBD) in patients with technically suboptimal echocardiograms under rest conditions.[2-6]

The microbubbles have thin and relatively permeable shells and typically are filled with a high-molecular-weight gas (eg, perfluorocarbon [PFC]) that slows diffusion and dissolution within the bloodstream. After intravenous (IV) injection, the microbubbles transit rapidly through the lungs, cardiac chambers, and myocardium, without any clinical effect on LV function, coronary or systemic hemodynamics, ischemic markers, or pulmonary gas exchange. Optison (GE Healthcare, Princeton, NJ), with a shell derived from human serum albumin, was the first PFC-containing IV ultrasonographic contrast agent approved for LVO and EBD use in humans. Definity (Lantheus Medical Imaging, North Billerica, MA) has also received FDA approval for LVO and EBD. Definity is a lipid-coated microbubble formed from 2 components, a long-chain lipid and an emulsifier, that are combined by agitation in a vial pressurized with PFC gas. This mixture is activated (Vialmix; Lantheus Medical Imaging) before use. The design characteristics of these agents are intended to preserve gas within the bubble to increase the duration of opacification.

None of these agents is yet approved by the FDA for assessment of myocardial perfusion. However, 2 additional agents, CARDIOsphere (POINT Biomedical Corporation, San Carlos, CA) and Imagify (Acusphere, Watertown, MA), have been evaluated in phase 3 pivotal studies for their indication in the diagnosis of coronary artery disease (CAD) by evaluation of myocardial perfusion, and both have been found to be noninferior to nuclear single photon-emission computed tomographic imaging.[7] One of these manufacturers(Acusphere) is seeking FDA approval for this indication at the time of this publication. Both agents are synthetic polymer-coated microspheres.

CARDIOsphere has an albumin and polylactide shell, which has sufficient thickness to be stable in the bloodstream even though the encapsulated gas is nitrogen, which has high solubility in blood. CARDIOsphere's particular structure, with a relatively stiff, brittle shell and rapidly diffusing gas, makes it suitable for intermittent harmonic power Doppler imaging at higher levels of mechanical index (MI). Imagify has both a synthetic, biodegradable polymer shell and a slowly diffusing encapsulated gas (decafluorobutane) that improves microbubble persistence within the bloodstream and renders it suitable for low-MI insonation. The requirements of myocardial perfusion by echocardiography are different from those of LVO. This perfusion technique requires the ability to deplete a myocardial region of microspheres by a pulse of ultrasound and then assess the rapidity of replenishment as a surrogate for myocardial blood flow, akin to a negative indicator dilution bolus. In this way, semiquantitative and quantitative image interpretation can be performed.

CONTRAST-SPECIFIC ULTRASOUND IMAGING

Although PFC gases and improved microbubble shell designs made ultrasound contrast agents more stable in the bloodstream, the ability of conventional echocardiographic imaging systems to detect them within the cardiac cavities and myocardial tissue was limited. The development of harmonic imaging, intermittent imaging, harmonic power Doppler, and, more recently, low-MI pulsing schemes has dramatically enhanced the ability to detect intravenously injected microbubbles in echocardiographic studies and to improve the duration of opacification. These methods all have in common the aim to detect the echo from bubbles and suppress the echo from tissue; they rely on the unique nonlinear behavior of a bubble in an acoustic field, the understanding of which is a prerequisite to a successful contrast study in the echocardiography laboratory.[1] Current commercially available ultrasound scanners have prespecified vendor presets that are generally suitable to yield good LVO.

Microbubbles in an ultrasound beam undergo resonant oscillation in response to the variations in acoustic pressure transmitted by the transducer. While the bubble oscillates, it is more stiff when compressed and less stiff when expanded. As a result, the radius of the bubble changes asymmetrically, and the reflected sound waves contain nonlinear components at multiples of the insonifying frequency. The creation of these microbubble "higher harmonics" yielded the first and most simple of the imaging methods, harmonic imaging.[8] Currently, harmonic imaging with contrast is rarely used in isolation because it is confounded by the tissue harmonic, which is created by nonlinear propagation of sound in tissue and results in incomplete suppression of the tissue echo. Indeed, the strength of the nonlinear components depends on the acoustic intensity, or MI, of the sound field.[9] Ultrasound imaging systems are required to provide a continuous display of the estimated MI used for imaging. The MI is a standardized estimate of the peak acoustic intensity, defined as the peak negative pressure [in megapascals] divided by the square root of the transmit frequency [in megahertz]. It should be noted that although a single MI value is estimated for a whole image, in reality it varies with depth and lateral location within the field of view. With use of a standard cardiac transducer at an MI > 0.1, most contrast microbubbles produce an echo with strong nonlinear components (Figure 1A). The role of the different contrast imaging modes is to create and detect these nonlinear components and display an image formed from them while suppressing the linear echoes from tissue and tissue motion.

Different techniques may be used to create bubble-specific images. High-MI methods rely on the fact that ultrasound, when applied at intensities commonly used in conventional imaging, disrupts and eliminates most microbubble contrast agents. Indeed, continuous imaging in harmonic mode at high MI results in destruction of microbubbles and creates a "swirling" artifact (Figure 1B, and Supplementary Figure 1 and Supplementary Movies 1 and 2). This feature can be used to the sonographer's advantage, however, with intermittent imaging, because the destruction effect is rapid (normally within a few microseconds). A technique such as power Doppler, designed to detect changes due to blood flow, interprets the change that occurs when bubbles are disrupted as a Doppler shift by displaying a bright signal in the echocardiographic image at the location of bubble disruption[10] (Figure 1C). Another approach uses harmonic imaging and subtraction of the predisruption image from the postdisruption image, and yet another approach detects the ultraharmonics (at 1.5 times the transmitted frequency) scattered by a disrupting bubble.

The advantage of higher MI methods is that they are sensitive to bubbles and thus effective for myocardial perfusion imaging.[11] They yield a high signal-to-noise ratio, reduce artifact, and facilitate strict image interpretation criteria for perfusion assessment that is based on duration of time required for replenishment. The disadvantage for LVO and EBD is that immediately after the image is made, the tracer has disappeared in the tissue, and a replenishment time of ≥ 1 cardiac cycle must elapse before another image can be made. Image acquisition is generally triggered to the electrocardiogram, and the mode is referred to as intermittent triggered imaging.[12] Clearly, the wall motion information from the echocardiographic image cannot be gleaned when in intermittent triggered imaging mode, because the frame rate is extremely low.

Real-time imaging of wall motion with LVO can only be achieved with methods that can detect bubbles without disrupting them, as occurs with low-MI imaging (Figure 1D, and Supplementary Figure 2 and Supplementary Movies 2 and 3). Thus, only the low-MI modes described below are relevant to the FDA-approved indication of LVO and EBD. The MI is held below 0.2, and a sequence of pulses is sent along each scan line, with each pulse differing in phase or amplitude, or both. The resulting stream of echoes is then processed so that when added together, the echoes from linear scatterers, such as tissue, cancel out completely, leaving only those from nonlinear scatterers, such as the bubbles. These pulse inversion or amplitude modulation techniques can be extended to include filters that eliminate tissue motion, so that bubbles can be detected in real time, even in the moving myocardium.[13] The disadvantage of low-MI modes is only relevant to the assessment of myocardial perfusion. These low-MI modes are less sensitive to bubbles than high-MI imaging. The advantage of low-MI perfusion imaging is that it can be used in a continuum of evaluation of wall motion and perfusion assessment (Figure 1E, and Supplementary Figure 3 and Supplementary Movie 3). The names given to these methods by their various manufacturers are summarized in Table 2.

Disruption of microbubbles at high MI can also be used to measure flow at the tissue level and forms an integral part of the assessment of myocardial perfusion. When microbubbles are administered as a continuous infusion and a steady level of enhancement is achieved by recirculation of the contrast agent, a high-MI pulse (or series of pulses) is applied, disrupting the bubbles in the imaging frame. New bubbles then replenish the imaging frame from adjacent tissue, and the rate at which they do so is proportional to the total flow of blood in the image, including microvascular flow. Areas of hypoperfused myocar-

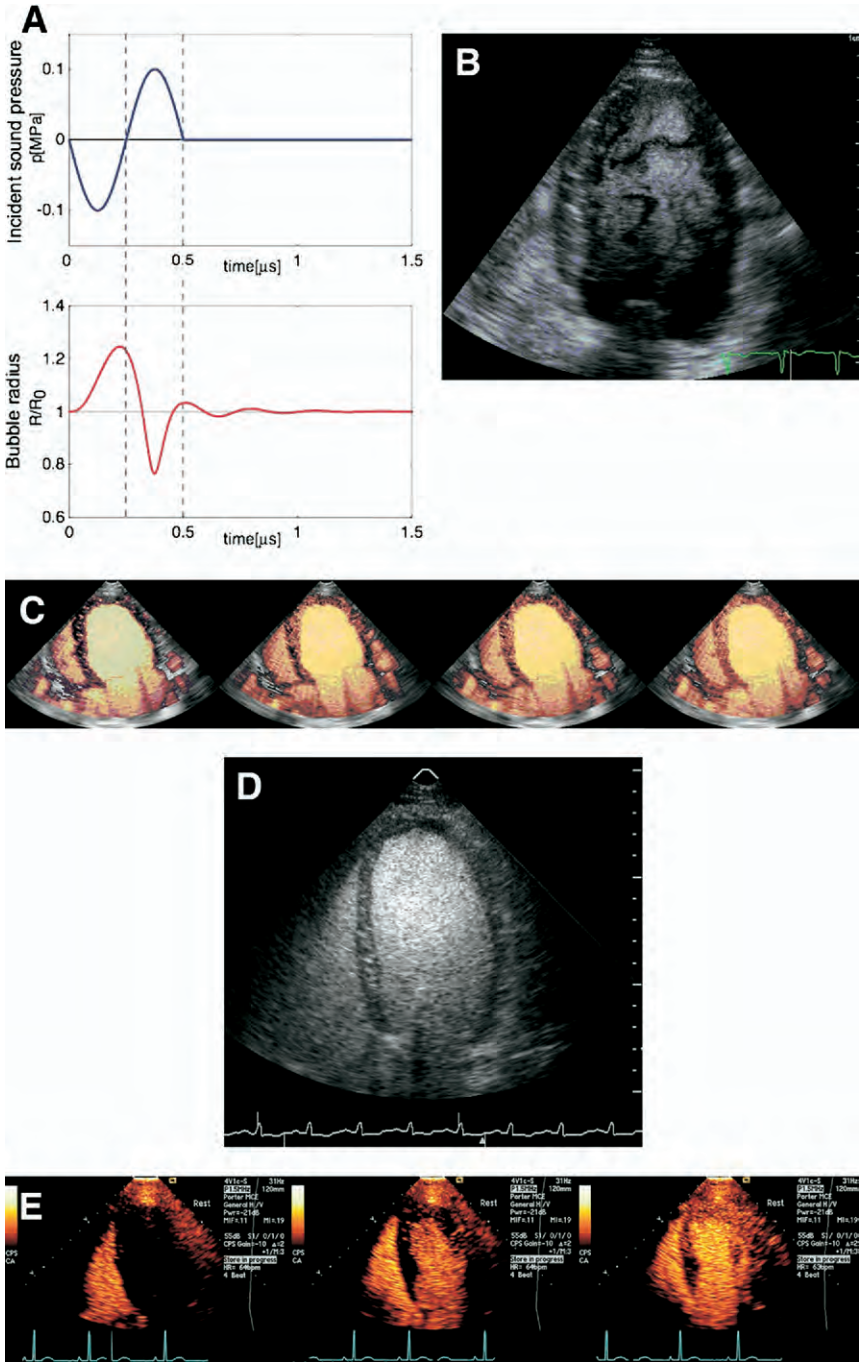

Figure 1 (**A**) Nonlinear bubble oscillation. When a microbubble is exposed to an acoustic field, its radius responds asymmetrically to the sound waves, stiffening when compressed and yielding a smaller change in radius. During the low-pressure portion of the sound wave, bubble stiffness decreases and radial changes can be large. This asymmetrical response leads to the production of harmonics in the scattered wave. (**B**) Pulse inversion image of LVO at high MI. Image shows the swirling artifact due to bubble disruption. (**C**) Disruption-replenishment perfusion imaging. High-MI intermittent power Doppler imaging of the left ventricle at pulsing intervals of 1, 2, 4, and 8 heartbeats. The myocardium enhances with increasing pulsing intervals, at a rate that reflects the blood flow rate of its perfusion. (**D**) Pulse inversion image of LVO at low MI. Uniform enhancement of the bubbles in the left ventricle is evident. (**E**) Low-MI, real-time imaging with contrast pulse sequencing to assess myocardial function and perfusion. Still-frame, apical 4-chamber images that were sequentially acquired *(left to right)* show contrast enhancement for function and perfusion assessment. *Left panel* shows start of IV injection of contrast agent, with the contrast medium entering the right ventricle. *Center panel* shows contrast within the LV cavity during the LVO phase, with clear endocardial border delineation. *Right panel* shows the myocardial phase with contrast seen in the myocardium.

Table 2 Microbubble-specific imaging modes

Imaging mode	Also known as	MI	
		High	Low
Harmonic power Doppler	Harmonic color power angiography; power harmonics	Yes	No
Harmonic imaging	—	Yes	No
Ultraharmonic imaging	1.5 harmonic imaging	Yes	No
Pulse inversion	Phase inversion; coherent contrast imaging; pulse subtraction	Yes	Yes
Pulse inversion Doppler	Power pulse inversion	No	Yes
Amplitude modulation	Power modulation	No	Yes
Phase and amplitude modulation	Contrast pulse sequencing	No	Yes

dium fill less quickly, so that at 1 second after a disruption pulse, for example, an area with a perfusion defect appears less bright on the image. This is the basis for the use of contrast enhancement in perfusion stress echocardiography. This technique can also be used to estimate the velocity and relative volume of blood in the myocardium. Originally, the method was described for high-MI imaging, where incremental intervals between high-MI image frames are triggered to the electrocardiogram.[14] Now, the replenishment can be imaged in real time, after high-MI disruption, using low-MI imaging.[15]

A. CLINICAL APPLICATIONS

The use of contrast agents for LVO improves the feasibility, accuracy, and reproducibility of echocardiography for the qualitative and quantitative assessment of LV structure and function at rest and during exercise or pharmacologic stress.[16-20] The use of contrast enhancement facilitates the identification and assessment of intracardiac masses, such as tumors and thrombi[16]; improves the visualization of the right ventricle and great vessels[17,18]; and enhances Doppler signals used for evaluating valvular function.[19,20]

Ultrasound contrast agents also have been effectively used in echocardiographic studies performed in the emergency department, ICU, interventional cardiology suite, and operating room. The efficient implementation of contrast medium use in the echocardiography laboratory results in procedural optimization and cost-effectiveness and may contribute to improved patient care outcomes.[21,22]

1. Assessment of Cardiac Structure and Function

It has been more than a decade since the first reports of successful LVO after the IV injection of air-filled microbubble contrast agents. During the past 5 to 10 years, improvements in ultrasound technology (including strategies of harmonic imaging and multipulse, low-MI imaging) and the commercial production of more robust contrast agents have resulted in routinely achievable persistent LVO and consistent improvement in EBD, which is pivotal to accurate evaluation of LV function. Clinical trials have shown that suboptimal echocardiograms (defined as nonvisualization of at least 2 of 6 segments in the standard apical echocardiographic views) can be converted to diagnostic examinations in 75% to 90% of patients; initially, fundamental and, later, harmonic imaging equipment was used.[2-6] Because of the creation of tissue harmonics and the improvement of image quality during high-MI harmonic imaging alone, even without use of contrast agents, fundamental imaging is now rarely used.

The use of echocardiographic contrast agents for LVO is particularly helpful when standard resting echocardiographic imaging is unyielding, which often occurs in patients who are obese, have lung disease, are critically ill, or are receiving ventilator care. Despite optimization of transducer frequency, sector width, and focus position, image quality can stay suboptimal in these patients unless a contrast agent is used. These technical challenges are accentuated during peak stress echocardiographic image acquisition, during which the use of a contrast agent has been shown to substantially benefit the yield of the study by improving image quality, confidence of interpretation, and accuracy.[23-25] Contrast agent use improves reproducibility and the accuracy of image interpretation for both experienced and inexperienced readers.[26]

i. Quantification of LV volumes and LVEF. The accurate determination of LVEF is critically important for managing patients with cardiovascular disease, and it has prognostic value for predicting adverse outcomes in patients with congestive heart failure, after myocardial infarction, and after revascularization.[27-30] Echocardiography is uniquely suited for the serial assessment of cardiac function, because of the absence of ionizing radiation and the easy accessibility, portability, and relatively low cost compared with other imaging techniques. Unfortunately, prior studies have found that conventional noncontrast echocardiography may have significant variability compared with accepted gold standards, with resultant low interobserver agreement. This variability has limited the applicability and the reliability of echocardiography for ventricular function measurements.

However, several recent studies indicate that contrast-enhanced 2D echocardiography has excellent correlation with radionuclide, magnetic resonance, and computed tomographic measurements of LV volumes and LVEF,[31,32] with improved interobserver agreement and physician interpretation confidence. Figure 2 shows the increasing accuracy of LVEF measurements when harmonic imaging and contrast imaging are used to improve border definition.[33] The accurate determination of LVEF is critically important in clinical decision making to determine the need for placement of intracardiac defibrillators and biventricular pacing systems. Emerging ultrasound technologies, including automatic quantification of LV structure and function with various edge detection and blood-pool algorithms, as well as 3-dimensional echocardiography, are enhanced by using IV echocardiographic contrast agents.[34,35]

Echocardiography is one of several techniques, including cineventriculography, radionuclide ventriculography, computed tomographic angiography, and magnetic resonance imaging, that have been used to determine LV volumes and LVEF. Although echocardiography is the most frequently used method in clinical practice, it has been slow to gain acceptance in clinical trials because of its moderate reproducibility and its limited accuracy to define LVEF in serial studies. Apart from inherent limitations of ultrasound imaging, which include image plane positioning, translational motion of the heart, and geometric assumptions, limitations in reproducibility and accuracy can be attributed to inadequate EBD. Contrast-enhanced

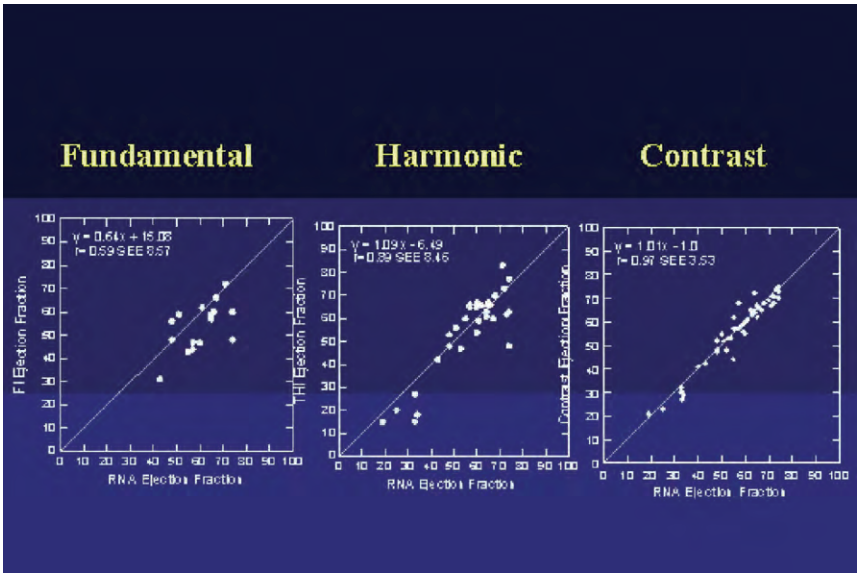

Figure 2 Contrast and quantitative assessment of LV systolic function. Comparison of ability to calculate LVEF with fundamental, harmonic, and contrast echocardiography. *FI*, Fundamental imaging; *RNA*, radionuclide angiography; *SEE*, standard error of the estimate for correlation; *THI*, tissue harmonic imaging. Adapted with permission from Yu et al.[33]

Table 3 Incremental accuracy of contrast echocardiography in the determination of LV volumes and LVEF

				Accuracy measured by linear correlation and corresponding SEE					
				UEE			CEE		
Study	Patients (n)	Gold-standard test	Echocardiographic parameter	*r*	SEE	Gold standard, mean ± SD*	*r*	SEE	Gold standard, mean ± SD*
Hundley et al (1998)[37]	35	MRI	LVEF	0.85	9%	−8 ± 6%	0.93	6%	+5 ± 3%
			LVEDV	0.92	21 mL	−21 ± 13 mL	0.95	15 mL	+15 ± 14 mL
			LVESV	0.94	25 mL	+17 ± 13 mL	0.97	20 mL	+12 ± 9 mL
Yu et al (2000)[33]	51	RNV	LVEF	0.59,†	8.6%,†	−6 ± 9%,†	0.97	3.5%	−0.3 ± 4%
				0.89‡	8.5%‡	−1 ± 8%‡			
			LVEDV	0.61,†	22.8 mL,†	−28 ± 65 mL,†	0.93	18.6 mL	−10 ± 40 mL
				0.71‡	31.8 mL‡	−38 ± 82 mL‡			
			LVESV	0.83,†	12.0 mL,†	−5 ± 30 mL,†	0.97	10.0 mL	−2 ± 17 mL
				0.89‡	23.5 mL‡	−10 ± 54 mL‡			
Dias et al (2001)[36]	62	RNV	LVEF	0.76,†	7.6%,†	−4 ± 8%,†	0.82	6.1%	−3 ± 6%
				0.74‡	7.3%‡	−1 ± 7%‡			
Hoffmann et al (2005)[38]	120	MRI, Cine V	LVEF	0.60,§	NR	+0.8 ± 11%,§	0.77,§	NR	+4.6 ± 8.7%,§
				0.72‖		−5.3 ± 13%‖	0.83‖		−2.1 ±10.3%‖
			LVEDV	NR	NR	−72 ± 40 mL,§	NR	NR	−42 ± 37 mL,§
						−72 ± 84 mL‖			−40 ± 37 mL‖
			LVESV	NR	NR	−36 ± 33 mL,§	NR	NR	+27 ± 27 mL,§
						−29 ± 51 mL‖			−16 ± 53 mL‖

CEE, Contrast-enhanced echocardiography; *Cine V*, cineventriculography; *LVEDV*, LV end-diastolic volume; *LVESV*, LV end-systolic volume; *MRI*, magnetic resonance imaging; *NR*, not reported; *RNV*, radionuclide ventriculography; *SEE*, standard of error of the estimate for correlation; *UEE*, unenhanced echocardiography.
*Data were extracted from tables and Bland-Altman figures of the reports.
†Fundamental imaging.
‡Harmonic imaging.
§Interclass correlation coefficient for LVEF compared with MRI.
‖Interclass correlation coefficient compared with Cine V.

echocardiography defines the endocardial border better than unenhanced echocardiography[3,4,6] and, compared with unenhanced echocardiography in numerous single-center and multicenter studies, shows better agreement and reduction in intraobserver and interobserver variabilities in measured LV volumes and LVEF with the use of current reference standards, including cineventriculography, radionuclide ventriculography, electron-beam computed tomography, and magnetic resonance imaging[31,33,36-39] (Table 3).

The underestimation of cardiac volumes by echocardiography is nearly resolved when contrast agents are used.[33] These findings

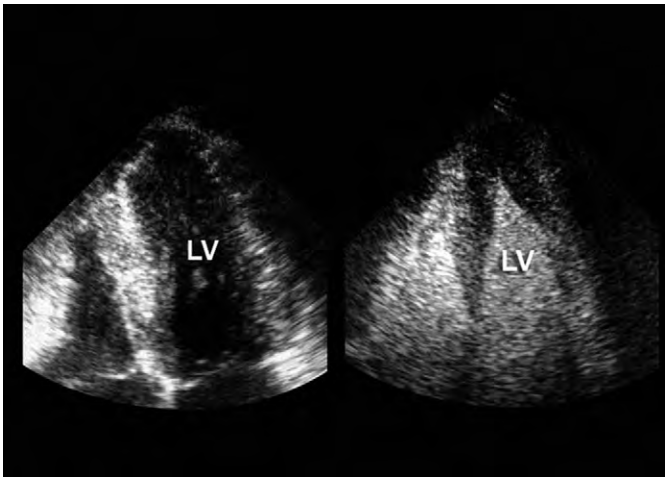

Figure 3 LV apical hypertrophic cardiomyopathy. Four-chamber noncontrast tissue harmonic image *(left and corresponding Movie File 1)* and contrast image *(right and corresponding Movie File 2)* at peak systole. Spadelike LV cavity contour is clearly defined in the contrast image, which is difficult to define on a noncontrast image. View video clips online.

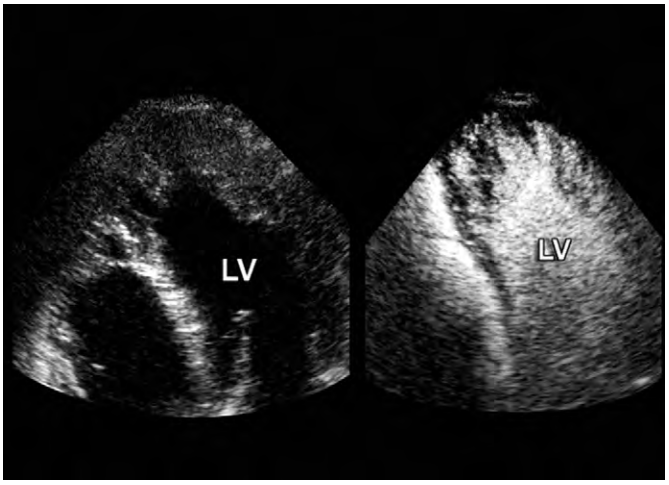

Figure 4 LV noncompaction with 4-chamber noncontrast tissue harmonic image *(left and corresponding Movie File 3)* and contrast image *(right and corresponding Movie File 4)* at end-diastole. The multiple deep trabeculations of the LV myocardium at the apex are clearly seen with contrast enhancement. View video clips online.

support the value of contrast echocardiography in serial assessment of LV systolic function.

Key Point 1: The accuracy of contrast echocardiography has been validated for the qualitative and quantitative assessment of LV function and volumes and should be considered in patients in whom precise information is clinically required, such as those undergoing serial assessment of LV function (patients undergoing chemotherapy or reevaluation of known heart failure with a change in clinical status, after myocardial infarction remodeling, after cardiac transplantation, or for the timing of valve replacement in valvular regurgitation) and those being evaluated for intracardiac device placement.

ii. Cardiac anatomy. Echocardiographic contrast agents also have been of value in the structural assessment of the left and right ventricles, the atria, and the great vessels. Contrast agents have a key role in definition of LV apical abnormalities, in complications of myocardial infarction, and in cases of intracardiac masses when nonenhanced images do not yield a definite answer.

LV apical abnormalities. Structural abnormalities of the LV apical region are often difficult to define clearly. Contrast-enhanced imaging enables clear identification of apical endocardial borders, which can facilitate diagnosis of these abnormalities.

LV apical hypertrophy. The apical variant of hypertrophy associated with hypertrophic cardiomyopathy is present in about 7% of affected patients but may not be detected by routine surface echocardiography (detection missed in about 15%) 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 spadelike appearance of the LV cavity, with marked apical myocardial wall thickening, is clearly evident on contrast-enhanced images[40] (Figure 3, Movie Files 1 and 2).

LV noncompaction. Noncompaction of the myocardium is an uncommon but increasingly recognized abnormality that can lead to heart failure and death. It is due to alterations of myocardial structure with thickened, hypokinetic segments that consist of 2 layers: a thin, compacted subepicardial myocardium and a thicker, noncompacted subendocardial myocardium. Contrast echocardiographic studies may be helpful in identifying the characteristic deep intertrabecular recesses by showing contrast medium–filled intracavitary blood between prominent LV trabeculations when LV noncompaction is suspected but inadequately seen by conventional 2D imaging[41] (Figure 4, Movie Files 3 and 4). It is useful to use an MI setting that is somewhat higher than for imaging with low MI (ie, 0.3-0.5) to most clearly delineate the trabeculations.

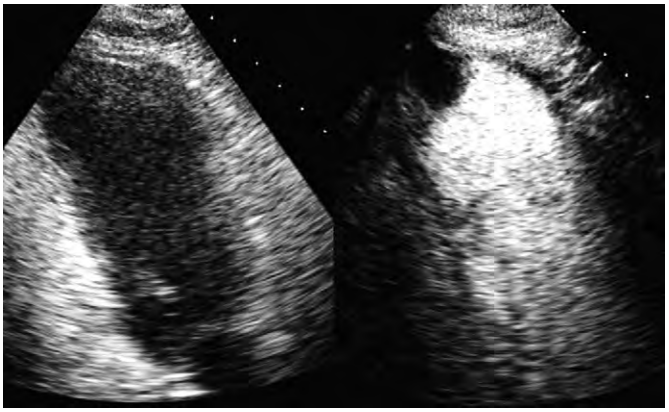

Figure 5 LV apical thrombus with 2-chamber noncontrast tissue harmonic image *(left and corresponding Movie File 5)* and contrast image *(right, and corresponding Movie File 6)* at end-diastole. View video clips online.

LV apical thrombus. The apex is the most common location for an LV thrombus. An apical thrombus may be difficult to define clearly, or to exclude, especially if the apex is foreshortened. However, contrast enhancement allows both complete visualization of the apical region by detection of contrast signal within the apex and optimization of transducer positioning and angulation to fully display the apical region. This technique reduces the likelihood of foreshort-

ening of the left ventricle and can be helpful in enabling visualization of the characteristic appearance of filling defect of a thrombus, if present[42] (Figure 5, Movie Files 5 and 6). On occasion, the thrombus may appear brightly echogenic (ie, white) before the administration of the contrast agent; in this case, if the usual grayscale settings are used during contrast enhancement, the echogenic thrombus may blend into the white of the opacified LV blood pool. Thus, it may be preferable to use harmonic power Doppler imaging. Further technical details on optimal imaging of thrombi are provided herein, in the section dedicated to LV masses.

LV apical aneurysm. LV aneurysm, an often asymptomatic complication of a prior myocardial infarction, is the most common apical LV abnormality. It is characterized by thin walls and a dilated apex, which may be akinetic or dyskinetic. These findings are usually seen easily on standard echocardiographic imaging. However, if the apex is foreshortened and not completely visualized, an apical aneurysm may go undetected. In addition, associated abnormalities (such as LV apical thrombus) may not be visible until a contrast agent is used.

Complications of myocardial infarction. LV pseudoaneurysm, free-wall rupture, and post–myocardial infarction ventricular septal defects usually pose a life-threatening risk to patients and can be detected by conventional echocardiography. However, patients may have suboptimal studies because of anatomy or position, or both, and clinical conditions (ie, being supine and intubated in the critical care unit) that limit the attainment of an optimal view of the apex. Contrast enhancement may be essential in establishing the diagnosis. Indeed, if clinically suspected, these diagnoses cannot be confidently excluded unless a contrast agent is administered to show the anatomy clearly, to outline abnormal structures, and to document the presence or absence of extracardiac extravasation of contrast agent.[43]

Abnormalities in other cardiac chambers. Although agitated-saline contrast medium 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 contrast agents have been used to show various abnormalities of right ventricular morphology, including dysplastic syndromes, tumor, and thrombi, and to distinguish these abnormalities from normal structures, such as prominent trabeculations or the moderator band.[17] Contrast medium has also been used to show anatomic features of the atria, especially the left atrial appendage, more clearly; it can be useful in differentiating thrombi from artifacts, dense spontaneous echocardiographic contrast, or normal anatomic structures.[44]

iii. Intracardiac masses. The detection and correct classification of intracardiac masses, including tumors and thrombi, are facilitated with the use of echocardiographic contrast agents.[16] The presence of a space-occupying defect in the LV cavity is the hallmark of an intracardiac mass and, when not clearly evident on baseline images, can be confirmed or refuted after injection of IV contrast medium. In addition, tissue characterization of the mass can be done simultaneously with standard, currently available commercial ultrasound imaging, which permits perfusion assessment. Contrast agents are administered intravenously at a constant rate to achieve a steady-state concentration, and imaging with either low-MI (power modulation or contrast pulse sequencing) or high-MI (harmonic power Doppler) strategies has allowed the assessment of perfusion of intracavitary masses. Qualitative (ie, visual inspection) and quantitative (ie, video-density detection software) differences in the gray scale between the levels of perfusion in various types of cardiac masses and sections of adjacent myocardium can be observed. Appendix A provides detailed methodology for Evaluation of Cardiac Masses Using Contrast Echocardiography. Most malignancies have abnormal neovascularization that supplies rapidly growing tumor cells, often in the form of highly concentrated, dilated vessels.[45] As a result, contrast hyperenhancement of the tumor (compared with the surrounding myocardium) suggests a highly vascular or malignant tumor.[16,46,47] Conversely, stromal tumors (such as myxomas) have a poor blood supply and appear hypoenhanced. Thrombi are generally avascular and show no enhancement. The level of contrast enhancement correlates with the diagnosis made by the gold standards of pathologic analysis or resolution of the mass after anticoagulant therapy. Although numerous echocardiographic criteria have been developed to define cardiac masses,[48-50] diagnostic errors have been reported,[51,52] and misclassifications can lead to unnecessary surgery or inappropriate anticoagulation.[53,54] The use of contrast agents to characterize cardiac masses can potentially avoid these unfortunate problems.

Key Point 2: Contrast echocardiography improves cardiac structural definition and should be considered in the following clinical situations when standard imaging does not yield diagnostic information:

- To document or exclude the following LV structural abnormalities
  - Apical hypertrophy
  - Noncompaction
  - Thrombus
  - Endomyocardial fibrosis
  - LV apical ballooning (Tako-Tsubo)
  - LV aneurysm
  - LV pseudoaneurysm
  - Myocardial rupture
- To identify and characterize intracardiac masses
- To assist in the differentiation of cardiac structural variants, such as apically displaced papillary muscles, and artifacts

iv. Extracardiac anatomy.

Vascular imaging. Accurate detection of vascular pathology, including dissection of the aorta and great vessels, atherosclerotic plaque, intima-media thickness, and detection of vasa vasora, can be facilitated with the use of echocardiographic contrast agents.[18,55-58] Contrast enhancement helps overcome limitations of vascular imaging because contrast agents augment backscattered signals from vascular structures. This applies for B-mode grayscale, as well as color and spectral Doppler modes.

Aortic dissection and other pathology. Although transesophageal echocardiography (TEE) continues to be the diagnostic method of choice for detection of aortic dissection, contrast enhancement has been shown to be useful in transthoracic examinations when this diagnosis is suspected and the intimal flap is difficult to visualize or there is uncertainty in distinguishing a flap from an artifact. In patients with aortic dissection or great-vessel dissection, or both, contrast enhancement helps delineate the true and false lumens. Ultrasound artifacts that mimic a dissection can be distinguished by the homogeneous contrast enhancement of the aorta. Administration of too large a contrast agent bolus or too rapid an injection should be avoided because it can result in attenuation, which in itself can result in or amplify artifacts. In select cases, the entry or exit point of the dissection may be identified, and extension of the dissection plane into major aortic branches (brachiocephalic, subclavian, celiac, or

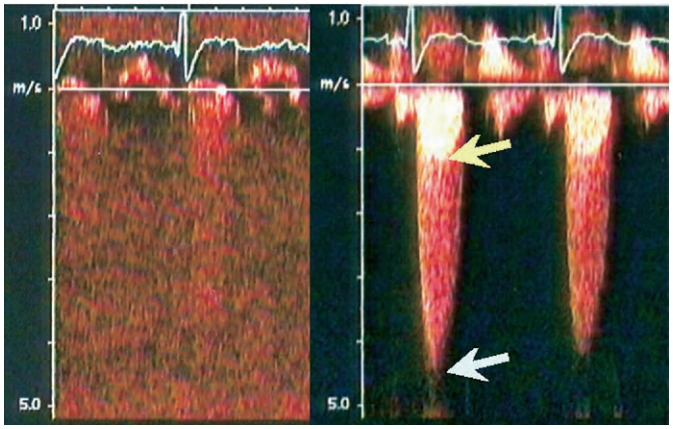

Figure 6 Contrast enhancement of aortic stenosis signal in a patient with a systolic murmur being evaluated for noncardiac surgical risk. Images show continuous-wave Doppler profile from apical window before *(left)* and after *(right)* contrast enhancement. The LV outflow tract spectral Doppler profile is clearly seen within the aortic valve spectral Doppler profile. Despite instrument optimization, the *left panel* shows only faint visualization of the velocity profile; the *right panel* after contrast enhancement shows not only peak transvalvular velocity *(white arrow)* but also subvalvular velocity *(yellow arrow)*.

renal) may also be visualized. Contrast enhancement also can be used in conjunction with TEE to clarify true and false lumens.

Femoral arterial pseudoaneurysms. Pseudoaneurysms of the femoral artery may occur as a vascular complication of cardiac catheterization and other invasive arterial procedures. Contrast enhancement assists in rapid assessment of the size and extent of these pseudoaneurysms, as well as in guidance of therapy.[59]

v. Doppler enhancement. Doppler echocardiographic assessment of blood flow velocities in the heart and the great vessels is a standard part of the cardiac ultrasound examination. Contrast enhancement of the Doppler signal has been shown to be of value when the signal is weak or technically suboptimal. Peak velocity measurement in patients with aortic stenosis may be enhanced with echocardiographic contrast agents[20] (Figure 6). Likewise, transmitral (rarely necessary) and pulmonary venous flow velocities used in assessing diastolic function can be improved with the IV injection of contrast agents.[19] Tricuspid regurgitant velocities (for assessing pulmonary artery systolic pressure) can be enhanced by either agitated bacteriostatic saline contrast or commercially available echocardiographic contrast agents. Usually, the contrast agent is used first for 2D imaging; because the threshold for detecting contrast by Doppler is far less than that for 2D imaging, Doppler signals can be acquired subsequently. However, the most distinct contrast-enhanced Doppler spectra may often be obtained at the very onset of the contrast injection. Care must be taken to avoid blooming of the signal, leading to overestimation of velocities; this blooming can be avoided by reducing the Doppler gain such that clear spectral envelopes are seen, without distortion along the edge of the profile.

2. Contrast Enhancement in Stress Echocardiography

Stress echocardiography is an established clinical tool with high sensitivity and specificity for the diagnosis of CAD through detailed evaluation of regional wall motion, cavity size, and LV function at rest and with stress induced by either exercise or pharmacologic means.[60-63] Stress echocardiographic results are also predictive of cardiovascular outcome in patients with normal[64] and abnormal[65-67] results. Because the detection of CAD with stress echocardiography is based on the observation of contractile dysfunction in any myocardial segment at rest or with stress, complete visualization of all LV endocardial borders is necessary to document or exclude abnormalities of regional myocardial wall thickening confidently.

However, stress echocardiography is not without limitations. Interpretation of wall thickening is qualitative, is highly dependent on the skill and experience of the reviewing physician, and is affected considerably by image quality. Numerous patient factors (such as body habitus and lung disease) may produce suboptimal images with poor EBD. Given, in addition, the challenges imposed by excessive cardiac motion due to hyperventilation and tachycardia, nondiagnostic or poor-quality images may occur in up to 30% of patients.[60] Furthermore, suboptimal studies result in increased interobserver variability and less reproducibility, with interinstitutional observer variance in stress echocardiographic interpretation reported to decline substantially (from 100% agreement for good image quality to 43% agreement in those studies with the lowest image quality).[68] The advent of digital side-by-side analysis, standardized reporting criteria, and generalized use of tissue harmonic imaging has reduced, but not overcome, this problem.[69]

The documented benefits of using contrast enhancement for LVO with resting echocardiography (ie, improved EBD, assessment of ventricular volumes and ejection fractions, recognition of wall-motion abnormalities, and enhanced reproducibility) clearly translate into benefits for stress echocardiography. Investigations using the earliest IV contrast agents showed incremental improvement in the reproducibility of stress echocardiography by producing greater than 80% improvement in EBD.[70] With current commercially available contrast agents, complete LV cavity opacification is reliably obtained (Figure 7, Movie Files 7 and 8), resulting in improvement in endocardial border resolution in up to 95% of patients at peak stress.[71] Compared with tissue harmonic imaging, contrast-enhanced imaging shows superior EBD at rest and peak stress across a range of image quality (greatest improvement is seen in patients with the poorest baseline images), where completeness of wall-segment visualization and reader confidence are highest with contrast enhancement, at both rest and peak stress.[24,25,72]

Several recent publications have addressed the critical clinical question of whether LVO actually improves the accuracy of stress echocardiography for diagnosis of CAD. The OPTIMIZE trial enrolled 108 patients who underwent 2 dobutamine stress echocardiographic studies, 1 with and 1 without contrast enhancement, in which the majority of patients had coronary angiography within 30 days.[25] As endocardial visualization and confidence of interpretation decreased in unenhanced studies, a greater impact of contrast enhancement on dobutamine stress echocardiographic accuracy was observed ($P < .01$). The agreement with angiography for diagnosing CAD increased by 31% in patients with poor visualization of the endocardium (>2 of 17 segments not visualized). This impact was more modest (5%) in patients in whom only 1 or 2 segments were not visualized. These findings support the ASE and American College of Cardiology recommendations for use of contrast enhancement in stress testing[73,74] and emphasize the importance of adequate visualization of segments for confidence of interpretation and accurate diagnosis.

In a larger study (229 patients) of contrast stress dobutamine echocardiography using coronary angiography as a gold standard, EBD and interobserver variability were superior with contrast en-

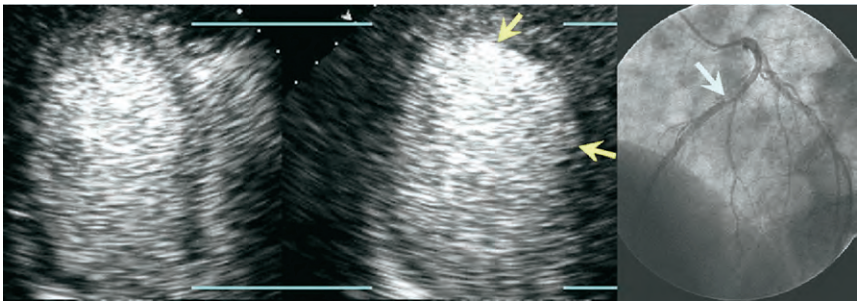

Figure 7 Exercise stress echocardiogram with contrast and subsequent coronary angiogram in a patient with exertional chest pain. *(Left panel and corresponding Movie File 7)* Exercise stress echocardiogram with contrast enhancement, apical long-axis views at end-systole. *Left view* is taken at rest; *right view* taken after stress. View shows LV cavity dilation and apical deformity (between *yellow arrows*) due to regional wall-motion abnormality in the mid to apical anteroseptal region on the poststress image. The *lower yellow arrow* shows hinge point in midanteroseptum. Findings are consistent with ischemia in the left anterior descending (LAD) coronary artery territory. *(Right panel and corresponding Movie File 8)* Coronary angiogram (left anterior oblique view) in same patient. Image shows high-grade mid-LAD artery stenosis *(white arrow)*. View video clips online.

hancement.[23] The use of contrast medium in patients with poor baseline images permitted the sensitivity, specificity, and accuracy for detecting coronary disease to become comparable to those for patients with good-quality, noncontrast resting images. Before contrast availability, poor image quality resulted in up to 20% of patients scheduled for stress echocardiography having nondiagnostic procedures or cancellations. Both of these results led to patients' being sent for other diagnostic methods.

From an economic standpoint, the use of contrast agents during stress echocardiography has been calculated to be cost effective,[21,75] with the cost of the contrast agent itself more than offset by savings incurred by reduction in downstream repetitive testing, by improved laboratory efficiency, and a lower rate of false-positive and false-negative diagnoses.

The decision to use contrast agents in stress testing is usually made at the start of the study, depending on image quality. However, in the event that image quality is good at baseline and deteriorates during stress, there is generally ample time and opportunity to administer contrast medium during a pharmacologic stress test (IV access in place and infusion of stressor occurring over 15-20 minutes). However, this is not the case during treadmill exercise stress echocardiography, which is the most commonly performed nonpharmacologic stress testing method. Detailed procedural recommendations for optimization of contrast agent use during stress echocardiography are summarized in Tables 4 and 5.

Key Point 3: Contrast echocardiography can convert a technically difficult, nondiagnostic stress echocardiogram into an accurate diagnostic study and avoid either an unachievable or a missed diagnosis. This obviates the need for alternative testing and improves efficiency, resulting in cost savings.

3. Echocardiography in the Emergency Department

A major advantage of echocardiography is that both global and regional cardiac function can be evaluated early in the triage of patients with chest pain presenting to the emergency department. The presence of regional wall-motion abnormalities on a resting echocardiogram has a high sensitivity for detecting cardiac ischemia in these patients.[76-79] Patients with regional wall-motion abnormalities were 6.1 times more likely to have cardiac death, acute myocardial infarctions, unstable angina, congestive heart failure, or revascularization within 48 hours of presentation ($P < .001$), and abnormal echocardiographic results were a more independent and incrementally useful prognostic indicator than clinical evaluation and electrocardiographic findings.[78] Conversely, patients with normal wall motion have a primary event rate (nonfatal acute myocardial infarction or total mortality rate) of only 0.4%.[79] In comparison, 2.3% of patients discharged from the emergency department after a routine evaluation may have acute myocardial infarctions.[80]

Contrast enhancement is not required for these studies but is indicated if regional wall-motion abnormality assessment is inadequate without it.[79,81] Although not currently approved by the FDA for this use, contrast echocardiography can also assess myocardial perfusion, which provides further incremental diagnostic and prognostic utility.[78,79] The combination of abnormal myocardial function and perfusion had an odds ratio of 14.3 for the development of an early event.[78] The FDA has recently revised its more restrictive black-box warning for contrast agents, to enable patients with suspected acute coronary syndromes to receive contrast medium, provided the patients also have additional monitoring (electrocardiographic single-lead tracing and pulse oximetry) for 30 minutes after contrast agent administration (see Section B below).[82] Patients with chest pain in the emergency department generally have such monitoring while being observed, so compliance with this requirement should be usual practice of care.

Key Point 4: Echocardiography in the emergency department can play a substantial role in the triage of patients with chest pain through the accurate diagnosis or exclusion of acute ischemic syndromes and the prediction of early and late cardiac events.

4. Contrast Agent Use in the ICU

Echocardiography has been the modality of choice for the diagnosis of cardiovascular disease in critical care settings, including the ICU. Important structural, functional, and hemodynamic information can be gleaned at the bedside, including evaluation of LV function. However, the feasibility of transthoracic echocardiographic imaging can be limited because of the often complex and dynamic profile of patients in the ICU, many of whom cannot assume an optimal position for imaging. Other obstacles that interfere with optimal echocardiographic imaging in the ICU include hyperinflated lungs due to mechanical ventilation, lung disease, subcutaneous emphysema, surgical incisions, chest tubes and bandages, crowded quarters, and poor lighting. As a result, endocardial resolution is frequently

Table 4 Guidelines for equipment setup and contrast agent administration

- Ultrasound machine settings
  - Preferably, use the low-MI preset provided by vendor of machine
  - MI ideally should be 0.15 to 0.3
  - Optimize transmit focus location (usually far-field location at level of mitral valve plane)
  - Optimize TGCs and gain
  - Minimize near-field gain
- IV setup and contrast agent preparation
  - Insert 20-gauge or larger angiocatheter into a large vein in the patient's forearm, preferably in the arm opposite the sonographer's imaging position; avoid the arm that has the blood pressure cuff
  - Avoid the antecubital vein for contrast studies performed with exercise, to minimize potential IV flow problems
  - When a quantitative contrast protocol requires simultaneous administration of a contrast agent and a pharmacologic stressor, both can be administered through the same line by using a 3-way stopcock. Ideally, have contrast line in parallel (not perpendicular) to pharmacologic stressor tubing; additional options include use of 2 IV access sites or a double-lumen angiocatheter
  - Store contrast agent as directed and check its expiration date before use
  - Before use, some contrast agents must be suspended or reconstituted. If the manufacturer's directions for preparing and injecting the agent are not followed, contrast visualization may be suboptimal. Therefore, prepare the agent in accordance with directions of package insert. Avoid exerting pressure against the contrast agent solution
  - Draw up the agent after venting the vial (or use a venting spike) and do not inject air
  - Depending on the individual contrast agent used, the agent may be given as an IV bolus, a diluted bolus, or an infusion (see below)
  - Often, it is useful to resuspend the contrast microbubbles immediately before injecting them with rolling the syringe or gently shaking the IV bag several times
- IV contrast injection, bolus method
  - Rest study
    - Rate of bolus injection is generally 0.5 to 1.0 mL/s
    - After bolus or diluted bolus injections, administer a slow saline flush (2-3 mL over 3-5 seconds)
    - When contrast agent is seen in right ventricle, stop flush
    - Administer additional IV doses as required
  - Stress study
    - Rest imaging: as above
    - Low-dose and peak dobutamine administration
      - Contrast agent can be injected through the dobutamine line
      - Use Y connectors and 3-way stopcocks
      - Avoid 90°-angle connections; avoid having IV line and blood pressure cuff on same arm
      - Dobutamine infusion acts as flush
      - If clinical events require termination of dobutamine infusion
        - Use saline flush (2-3 mL over 3-5 seconds)
        - If attenuation occurs, decrease injection rate or decrease infusion rate, or use high-power (high-MI) impulse to immediately decrease attenuation*
  - Peak exercise
    - While patient is on treadmill, inject contrast agent about 30 seconds before exercise termination
    - If patient is doing bicycle exercise, inject contrast agent at each stress stage (intermediate and peak) at which imaging will be recorded (about 2 minutes before image acquisition; eg, at beginning of stage if 2-minute stage, at 1 minute into stage if 3-minute stage)
    - Inject optimal rest dose with saline flush as described above
    - Transfer patient to imaging bed
    - Administer additional contrast agent as required with slow saline flush
  - If attenuation occurs, use high-power (high-MI) impulse to immediately decrease attenuation*
- IV contrast injection, infusion method
  - Dilute contrast agent in 9 mL of saline in a 10-mL syringe or a 50-mL bag of saline
  - Adjust infusion rate in accordance with the appearance of contrast image, generally 150 to 200 mL/h, if using the 50-mL bag of saline, or if using the 10-mL syringe, as a slow push of 0.5 to 1 mL every few minutes
  - Infusion pump (ideal) or hand push (acceptable) methods can both be used

TGC, time-gain correction.

*When low-MI imaging presets are used for LVO, the appearance of contrast medium in the myocardium may become so robust that clear endocardial border distinction between myocardium and the LV cavity may become obscured. This reduced image quality is managed by intermittent use of brief high-power frames ("flash" or "burst") to cause myocardial bubble depletion, which will be proportionately greater in the myocardium than in the LV blood-pool cavity, resulting in restoration of clear delineation between myocardium and LV cavity. See Supplementary Figure 4.

suboptimal, which prevents the accurate assessment of regional and global wall motion. Although TEE can overcome these limitations, transthoracic echocardiography with contrast enhancement is less invasive.

The use of contrast echocardiography overcomes several of the disadvantages associated with standard echocardiographic imaging in the ICU and can be beneficial for assessment of global and regional ventricular function. Several studies have demonstrated the safety

Table 5 Practical guidelines and ways to avoid common pitfalls when using contrast agents for image acquisition

Start at apical window and have the patient in a bed with a cutout
To improve image quality and decrease shadowing
Use respiratory movements
Move transducer to change its position (more laterally)
If shadowing cannot be eliminated, attempt to direct shadow through center of left ventricle
If apex is underfilled with contrast medium
Reduce MI
Inject more contrast medium
Use a higher volume and more rapid saline flush
Adjust transmit force to apex
If attenuation occurs
Wait a few seconds
Increase the MI
Use high-power impulse

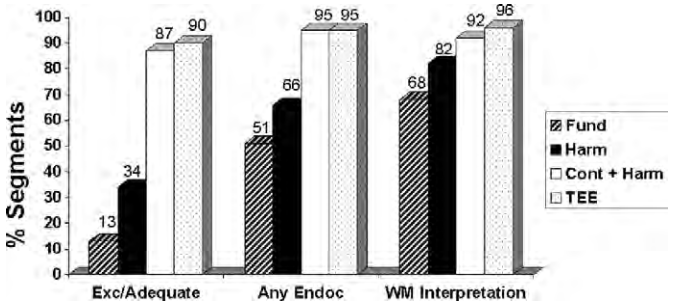

Figure 8 Comparative percentage visualization of segments and wall-motion (WM) interpretation with fundamental (Fund), second harmonic (Harm), and contrast with harmonic (Cont + Harm) visualization and TEE of patients with technically difficult TEE in the ICU. *Any endoc*, any endocardial visualization; *exc/adequate*, excellent/adequate visualization. Adapted with permission from *Yong et al*.[86]

and feasibility of contrast echocardiography in critically ill patients.[83-87] The administration of contrast medium with harmonic imaging leads to increased visualization of myocardial segments, which enhances the interpretation of regional and global LV function and allows the evaluation of cardiac function in otherwise suboptimal or uninterpretable studies.[83-86,88,89] Whereas tissue harmonic imaging enhances visualization of the endocardial borders and facilitates interpretation compared with fundamental imaging, the addition of contrast medium further improves visualization and interpretation of cardiac function compared with tissue harmonic imaging alone.[83-86] Improved endocardial visualization with contrast enhancement also translates into better diagnostic accuracy and cost-effectiveness. In a study that compared results with TEE in technically difficult ICU studies, the addition of contrast enhancement to harmonic imaging improved visualization of endocardial borders and allowed a more accurate estimation of wall motion and global function, with results similar to those achieved with TEE[86] (Figure 8). Contrast agent administration to patients in whom imaging would be technically difficult was also the most cost effective echocardiographic imaging method compared with fundamental imaging, harmonic imaging alone, and TEE.[86] Furthermore, contrast enhancement can be helpful in characterizing or confirming pericardial effusion with associated cardiac tamponade and aortic dissection (see section A.1.iv). However, contrast is not beneficial for evaluation of valvular structure in such situations as endocarditis or valvular regurgitation. In these cases and for suspected aortic dissection, TEE continues to be the primary echocardiographic diagnostic method of choice.

The availability of contrast imaging in the ICU enhances overall efficiency, diagnostic accuracy, and cost-effective patient management[83-86] and has no incremental risk for death compared with noncontrast echocardiography in ICU patients.[87] For patients with pulmonary hypertension or unstable cardiopulmonary conditions, the FDA has recently relaxed the prior black-box specification from a contraindication to a warning. The requirement for additional monitoring (single-lead electrocardiographic and pulse oximetry) in such patients continues for 30 minutes after contrast agent administration. However, in an ICU setting, patients generally have such monitoring while being observed, so compliance with this requirement should be usual practice of care.

Key Point 5: Contrast enhancement of transthoracic echocardiograms in technically difficult patients in the ICU can be used to provide bedside assessment of cardiac structure and function, recognizing that risk and benefit must be determined on an individual basis in critically ill patients and that appropriate monitoring must be available.

5. Contrast Agent Use in Cardiac Interventional Therapy

Alcohol septal ablation was introduced more than a decade ago for the treatment of patients with hypertrophic obstructive cardiomyopathy. During alcohol septal ablation, intracoronary ethanol is injected into one or more of the septal perforator arteries that supply the anterior septum and results in an acute deterioration of basal septal function creating an acute decrease in LV outflow tract gradient and in the severity of mitral regurgitation. Myocardial contrast echocardiography (MCE) has an important role in guiding alcohol septal ablation.[90-92] The method and technical details for Contrast Echocardiography-Guided Alcohol Septal Ablation for Hypertrophic Cardiomyopathy are summarized in Appendix B. Although it is true that clinical experience has proved the usefulness and safety of this procedure in 2,000 patients worldwide and, as such, this procedure has been clinically accepted, the intra-arterial injection of contrast agents remains contraindicated in the recent FDA relabeling for contrast agents. However, the use of agitated radiographic contrast agents is possible for the identification of target septal segments, with an acceptable degree of myocardial opacification.

Key Point 6: Direct intracoronary injection of contrast agents into suspected culprit septal perforator arteries during transthoracic echocardiographic monitoring has been used to identify the septal artery in patients with hypertrophic cardiomyopathy who are undergoing alcohol ablation for chemical myectomy. However, the FDA has stated that the intracoronary use of contrast agents is contraindicated.

6. Use of Contrast Agents in Pediatric Echocardiography

Ultrasound contrast is not approved by the FDA for use in pediatric patients because the safety and efficacy of contrast agents have not been established definitively in children. Although the reported clinical use of transpulmonary contrast agents in children is limited, the agents' utility in this population can be quite valuable.[93,94] Contrary to general belief, echocardiographic images in children are not always diagnostic. In addition, pediatric patients may not always be cooperative, and pediatric cardiologists have less training in re-

gional wall-motion interpretation during stress echocardiography than their counterparts in adult cardiology. These factors make contrast agents valuable in evaluating pediatric patients, particularly those who routinely undergo stress echocardiography (patients with Kawasaki disease[95] and those who have undergone the arterial switch operation, other coronary reimplantation surgery, and cardiac transplantation), because contrast agents facilitate endocardial identification. In patients with complex congenital heart disease, functional evaluation of the right ventricle is often necessary. Contrast agents can be helpful in endocardial definition of these geometrically unusual chambers, thereby aiding in function assessment. These patient groups include patients after procedures to repair tetralogy of Fallot and after the Senning and Mustard procedures, although most patients who have had these procedures are now adults.

The safe and effective dosage of contrast medium in children has not been definitively established. Furthermore, with significant intracardiac shunts, microspheres may bypass filtering by the pulmonary capillary bed and directly enter the arterial circulation, potentially resulting in microvascular obstruction. Therefore, it is recommended that commercial contrast agents not be used in the presence of significant intracardiac shunts unless the clinical benefits outweigh the potential risk. For the same reason, it is believed that contrast agents should not be administered to patients with significantly elevated pulmonary vascular resistance.

Key Point 7: Contrast use in pediatric patients has not been associated with adverse effects when used in patients without significant intracardiac shunts or severely increased pulmonary vascular resistance and can be helpful in patients in whom the benefit of enhanced endocardial definition for cardiac structural assessment is clinically indicated, although not approved by the FDA for this indication.

B. SAFETY OF ECHOCARDIOGRAPHIC CONTRAST AGENTS

A large body of relevant published clinical data establishes the safety of approved and experimental ultrasound contrast agents.[2,96-106] These studies have primarily been performed under conditions of rest and stress in patients with known or suspected CAD. The FDA has monitored the designs of many of these studies and has approved 3 agents for cardiac indications after extensive clinical trial experience that involved detailed safety evaluations, including direct comparisons with placebo that showed no significant difference in total or specific adverse events.[6] Initial postmarketing approval surveillance over a 5-year experience and >1 million patient studies provided no medically significant risks apart from rare allergic events at an approximate rate of 1 per 10,000. Adverse effects have been reported for all approved agents; they are usually infrequent and mild and may include headache, weakness, fatigue, palpitations, nausea, dizziness, dry mouth, altered sense of smell or taste, dyspnea, urticaria, pruritus, back pain, chest pain, or rash, or a combination of these effects. However, allergic and potentially life threatening hypersensitivity reactions may occur rarely, including anaphylactoid and/or anaphylactic reactions, shock, bronchospasm, tongue and/or throat swelling, decreased oxygen saturation, and loss of consciousness. These events are probably related to non–immunoglobulin E–mediated or anaphylactoid reactions from local complement activation.[107,108] Since the initial approvals, it has been recommended that patients should be closely monitored for hypersensitivity reactions and diagnostic procedures should be carried out under the direction of a physician experienced in the management of hypersensitivity reactions, including severe allergic reactions, which might require resuscitation. Serious central nervous system reactions, including seizures, seizurelike reactions, and altered consciousness, have also been reported rarely and may or may not be associated with immediate hypersensitivity reactions.

Initial contraindications for Optison and Definity (the 2 clinically used agents in the United States) reflected only known allergy to the components of the microbubbles and known intracardiac shunts (other than patent foramen ovale). The fact that certain groups of patients, such as those with severe arrhythmias, pulmonary hypertension, and heart or liver failure, had not been systematically included in large clinical trials had warranted a cautionary advisory to the use of echocardiographic contrast agents in these patient groups. Although several clinical trials have shown no evidence of significant change in pulmonary artery pressures, resistance, and gas exchange when clinically recommended dosages of contrast in patients with chronic obstructive pulmonary disease, diffuse interstitial pulmonary fibrosis, and congestive heart failure,[109] it was advised that special care be taken for patients with small pulmonary vascular beds, severe emphysema, pulmonary vasculitis, or histories of pulmonary emboli and pulmonary hypertension.

In 2004, the European Agency for the Evaluation of Medicinal Products (EMEA) reviewed the postmarketing surveillance data that referred to more than 150,000 vials of the contrast agent SonoVue (Bracco Diagnostics, Milan, Italy)[110] and temporarily withdrew the approval of SonoVue for cardiac applications. Three deaths had been reported in temporal relation with the application of SonoVue. There was no evidence of an allergic reaction in these patients, but all of them had unstable ischemic heart disease. Nineteen cases of severe, nonfatal adverse events (0.002%) were reported, and most of the cases were considered to be allergic reactions. After reviewing the fatal and nonfatal serious adverse events, the EMEA committee recognized that there was a favorable risk/benefit ratio for SonoVue when patients with acute coronary syndromes and unstable heart disease were excluded, and the committee otherwise restored the approval for cardiac indications.

Even more recently, the FDA reviewed its guidelines on the safety of echocardiographic contrast agents and issued a black-box warning for Definity in October 2007.[82] The warning was based on postmarketing reports of deaths in 4 patients with significant underlying progressive cardiovascular disease that were temporally related to contrast agent use and approximately 190 other, variably characterized nonfatal adverse events, without conclusive evidence of causality. These reports extended over 6 years, during which approximately 2 million patient doses of contrast medium were administered, with a mortality rate of approximately 1 per 500,000. Previously, occasional intolerance characterized primarily as back pain, headache, or urticaria and, rarely, anaphylactic allergic reactions (estimated rate, 1 per 10,000) had been reported. The black-box warning applied to the class of perflutren-containing ultrasound contrast agents (ie, Definity and Optison), contraindicating their use in patients with acute myocardial infarctions and worsening or clinically unstable heart failure. Additional contraindications included serious ventricular arrhythmias or high risk for arrhythmia; respiratory failure as manifest by signs or symptoms of carbon dioxide retention or hypoxemia; severe emphysema, pulmonary emboli, or other conditions that cause pulmonary hypertension due to compromised pulmonary arterial vasculature; and intra-arterial injection. These new contraindications were added to the existing contraindications that were placed at the time of initial approval:

- right-to-left, bidirectional, or transient right-to-left cardiac shunt, and
- hypersensitivity to perflutren.

Additionally, monitoring of all patients receiving contrast medium was required for 30 minutes after administration, including vital sign measurements and electrocardiography in all patients and cutaneous oxygen saturation in patients at risk for hypoxemia. As initially advised, the requirement for ready availability of resuscitation equipment and trained personnel remained in place.

There was widespread concern in the medical community over these new contraindications and requirements, which did not take into account the proven efficacy of ultrasound agents, the previously established safety of these compounds, the potential risks of the alternative procedures, and the likely confounding effect of pseudocomplication in the reported events.[111-113] This concern stimulated the FDA to review these new requirements, and subsequently, on May 12, 2008, and June 6, 2008, revised labeling changes were again implemented for Definity and Optison, respectively, reflecting a substantial relaxation of the previously imposed limitations by the removal of the expanded contraindications and their replacement with warnings instead (http://www.fda.gov).[82] In summary, the present FDA documents for both Definity and Optison state **that these products are not to be administered to patients in whom the following conditions are known or suspected:**

- right-to-left, bidirectional, or transient right-to-left cardiac shunts;
- hypersensitivity to perflutren; and
- hypersensitivity to blood, blood products, or albumin (applies to Optison only).

The intra-arterial injection of ultrasound contrast agents also is contraindicated. Importantly, additional monitoring of vital signs, electrocardiography, and cutaneous oxygen saturation (for 30 minutes) is not required in all patients but is now limited to patients with pulmonary hypertension (degree not specified) or unstable cardiopulmonary conditions.

The potential for adverse bioeffects from contrast agents in an ultrasound field has also raised concern about the agents' clinical use.[114,115] Experimental studies on small animals and cell preparations have shown that dose-dependent bioeffects (hemolysis, platelet aggregation, disruption of cell membranes, rupture of small vessels, and induction of ectopic beats)[116-118] can be induced under certain extreme conditions (exteriorized heart preparation, no or minimal attenuation, low-frequency high-acoustic pressures, long pulse durations, and vastly excessive doses of contrast agent per tissue volume). These experimental findings cannot be extrapolated to the clinical setting where the attenuation of ultrasound significantly reduces patient exposure. Indeed, these conditions potentially exist clinically only during lithotripsy and focused ultrasound ablation procedures. The current thresholds for diagnostic ultrasound imaging take into account the dose dependency of ultrasound bioeffects, and, in ultrasound scanners approved for clinical use, bioeffects due to ultrasound appear to be clinically irrelevant.[9] Thus, there is no evidence that maximum approved clinical doses or maximum approved transmit power, or both, are associated with any bioeffects. Similarly, only one publication reporting use of a noncommercially available research microbubble has shown provocation of isolated premature ventricular contractions using end-systolic triggering at an MI of 1.6 and with bolus dosing.[119] This agent is no longer in clinical development. No premature ventricular contractions were seen at an MI of $\leq$1.1 or with diastolic triggering. Several clinical studies have shown a lack of arrhythmia provocation for both high-MI and low-MI settings and triggered imaging. Minor prolongation of the QT interval has been observed during phase 3 trials of Definity, but this finding seems to be without clinical relevance. Large clinical trials of ultrasound contrast agents administered with triggered ultrasound at MI of $\leq$1.0 for expanded cardiologic indications have been completed to further assess the potential for cardiac arrhythmia and have not indicated concerns.[101-103,120]

C. ECHOCARDIOGRAPHY LABORATORY IMPLEMENTATION OF CONTRAST AGENT USE: A TEAM APPROACH

Because the use of contrast agents clearly increases the accuracy and diagnostic content of echocardiographic studies,[3,23,24,31-35,37,38] the routine use of contrast echocardiography depends to a large extent on the tolerance for inadequate or nondiagnostic studies, awareness of indications for contrast, and the ease of use of contrast.

Laboratories that have successfully introduced contrast agents have uniformly implemented a practice by which the sonographer, immediately at the time of study performance, identifies the need for their use.[22] Many laboratories have used a standing order that reflects precise indications and contraindications and is tailored to the administrative policies of their respective institutions.

The administration of contrast medium can be time consuming, and each laboratory should develop mechanisms to minimize delays. Coordination with a registered nurse or, alternatively, administration of the contrast agent by the sonographer (if qualified and permitted by the sonographer's hospital and by state regulations) is very important. Ready access to contrast agents is of critical importance, as is training of qualified personnel to inject contrast agents outside the echocardiography laboratory.

Sonographers, nurses, and physicians should be aware of the indications for a contrast study, and the echocardiography laboratory should develop a written protocol that describes indications, injection and imaging protocols, and personnel responsibilities. A well-informed member of the echocardiography team should explain the contrast agent injection to the patient, including a discussion of rationale, contraindications, and warnings. Using this approach, the usual practice in most echocardiography laboratories is to obtain verbal consent from the patient. However, depending on the policy of the local hospital or clinic, written consent may be used.

Key Point 8: Implementation of a contrast program requires a strong commitment to quality on the part of the medical director. Laboratories that have been successful in establishing contrast agent use have uniformly implemented a practice by which the sonographer, early at the time of the study, identifies the need for the use of a contrast agent, on the basis of a standing order that clearly describes its precise indications and contraindications.

1. Role of the Physician

The physician leaders are ultimately responsible for the adequacy and appropriateness of the echocardiographic studies performed in the echocardiography laboratory. The physician leader must mentor the group to work as a team, while setting an example of communication among the laboratory personnel working together to administer contrast agents (ie, sonographers, nurses, and, possibly, fellows).

It is the role of the physician to define the precise indications and contraindications for the use of contrast enhancement. Indications should be driven by quality; therefore, contrast enhancement may be deemed necessary if the clinical question posed is not answered with nonenhanced echocardiography. It is the physician's role not to be complacent with less than adequate studies and to stimulate other team members to do the same. This approach results in general agreement that nondiagnostic studies are not acceptable.

Physicians must gain experience in interpretation of contrast-enhanced studies. They must become familiar with the pitfalls and the artifacts and understand the details of contrast agent administration that could avoid these unwanted features. The provision of feedback to all members of the team (including sonographers and nurses) regarding the quality of the studies is essential.

2. Role of the Sonographer

As a member of the health care team, the sonographer has several roles to enhance the effective use of contrast medium.[121] The sonographer must have a thorough understanding of microbubble physics for equipment optimization and image acquisition, to aid in the development of departmental contrast medium protocols and procedures[122] and foster the implementation and administration of contrast agents when necessary. The sonographer is the first team member able to identify the need for contrast medium use in image acquisition. Most of the time, experienced sonographers can quickly determine whether a particular study will be diagnostic. This quick determination affords a good opportunity to decrease the total time used in performing a technically difficult study. The struggle time, or the time to make a study diagnostic, can be greatly shortened if the decision to use contrast medium is made promptly.[22] This prompt decision making can be done by initially performing a quick basic-4-view (apical 4 chamber, 2 chamber, and long axis and, optionally, parasternal long axis) check of LV visualization.[123] By decreasing the struggle time, the sonographer can decrease the total time allocated to perform a contrast-enhanced echocardiographic study to less than the time for a nonenhanced, technically difficult study.[22] If contrast enhancement is deemed necessary, an efficient approach is for the sonographer to perform the Doppler part of the examination while procedures for the establishment of IV access are under way. At the same time, a quick subcostal view may be done for color flow Doppler screening of the atrial septum to evaluate for potentially significant right-to-left shunting. Detailed methodologic recommendations and suggestions on how to avoid and overcome frequent pitfalls are summarized in Tables 4 and 5. In some laboratories, the sonographer is also responsible for starting the IV administration of contrast agent (see the following).

3. Role of the Nurse

The nurse is usually the team member who explains the use of contrast medium to the patient, including the discussion of potential side effects. In the absence of the nurse, this responsibility is the physician's. Alternatively, this function can be done, as detailed above, by any well-informed member of the echocardiography team and may be further supplemented or substituted with use of an informational brochure. Nurses often are the designated personnel to start the IV line after the decision has been made to use contrast enhancement. A nurse or a physician typically starts the IV administration of the contrast agent. However, in some laboratories, IV insertion and, in some cases, contrast agent administration have been incorporated into the sonographer's responsibilities after appropriate training. This approach is an acceptable one, provided that appropriate training and credentialing have been obtained.

Nurses need to be aware of the different ways of administering contrast agent (bolus and infusion) and their effects on the images produced. Familiarity with adequate dosing and artifacts such as swirling and attenuation, as well as the specific minimization and correction of artifacts, is of utmost importance for all team members. Frequent communication and dialogue between the nurse and the sonographer are essential to optimize contrast medium effect for the individual patient. Nurses should also be aware of contraindications to contrast agent use and the potential adverse effects of the contrast agent, including the management and reporting of adverse effects. Nurses also may have a role in the additional monitoring of patients with unstable conditions, now required after contrast agent administration. The nurse or whoever administers the contrast agent should document in the medical record the dose of contrast medium used and the time of administration.

4. Training Issues

For physicians, the basic prerequisites for independent competence in echocardiography (level 2 training) must be met before experience with contrast agents is initiated. Level 2 training is defined as including a minimum of 6 months of echocardiography education involving 300 studies with a wide variety of abnormalities.[124] Special competence in stress echocardiography training, as outlined by the ASE, is also recommended.[125] Cardiac sonographers should be well experienced and should be credentialed in echocardiography. Beyond these basic prerequisites, the use of contrast in rest echocardiography or stress echocardiography, or both, optimally requires a level of experience obtained through exposure and performance, initially with guidance and supervision. Physicians and sonographers are encouraged to pursue courses, tutorials, and preceptorships to learn the appropriate techniques for administering contrast agents and interpreting contrast-enhanced echocardiograms, to optimize the benefit to the patient. They also should ensure that equipment is optimized for contrast echocardiographic examination through discussion with the equipment manufacturers. Practitioners need to be competent in the administration of contrast agents, should be familiar with contraindications, and should be able to deal with any possible adverse effects. The determination of credentials and supervision required for administration of contrast agents (IV placement and injection of contrast agent) are to be guided by the individual institution's policies, which should adhere to local and state requirements.

It is anticipated that additional training will be required when contrast perfusion studies become a clinical reality, because certain techniques for LVO enhancement and perfusion assessment with high- and low-power imaging strategies have been uniquely developed. However, experience with LVO contrast enhancement is essential to the cardiac sonographer and echocardiographer as a foundation from which to begin as ultrasonic contrast methods are used increasingly to assess both function and perfusion.

5. Cost-Effectiveness

Early studies indicated that the substantial improvement in diagnostic accuracy afforded through use of contrast enhancement may contribute to a cost-effective pattern of care.[21,22,126] This pattern is achieved through (1) an impact on downstream repetitive testing in patients with an initially nondiagnostic echocardiogram,[127] (2) a reduced rate

of false-positive and false-negative echocardiographic results as a result of improved image quality, and (3) increased laboratory efficiency in evaluation of patients whose conditions are labor-intensive and difficult to image.

Key Point 9: Contrast agent use is reimbursable; the agents are cost-effective when used in an appropriate and efficient manner.

D. SUMMARY OF RECOMMENDATIONS FOR ULTRASONIC CONTRAST AGENT USE FOR ECHOCARDIOGRAPHY

A summary with details of the recommended applications is included in the synopsis at the beginning of this document. Contrast enhancement is an essential part of a modern, quality-driven echocardiography laboratory and administration of contrast agents is most effectively achieved by establishment of a sonographer-initiated decision-making process guided by a physician standing order that clearly describes the precise indications and contraindications for contrast-enhanced studies. The successful implementation of contrast agent use requires the effort of a team, optimally composed of physicians, sonographers, and nurses. The cost of contrast agent use is reimbursable (Appendix C); the appropriate and efficient use of contrast agents is recommended to promote cost-effectiveness. To ensure quality control and maximize benefit to patients, the ASE recommends that appropriately trained cardiac sonographers and physicians with level 2 or level 3 training, and the laboratories at their institutions, establish an effective system to enable use of contrast enhancement.

E. SPECIAL CONSIDERATIONS

Because optimal stress echocardiographic imaging is dependent on the quality of cardiac structural definition, the indications for contrast medium use in stress echocardiography are the same as for rest echocardiography. Specifically, contrast enhancement is indicated in difficult-to-image patients at rest when echocardiographic image quality does not permit adequate assessment of cardiac structure and function. Contrast enhancement for stress echocardiography is not recommended for every study but should be considered on a case-by-case basis, depending on image quality.[25] This recommendation is made on the basis of expert consensus opinion and in light of results of a recent study.[25]

Reference has been made to the recent FDA labeling and relabeling changes (October 2007 and May 2008) for PFC contrast agents in the relevant sections of this document, as well as in section B, dedicated to safety. Extensive discussions about appropriate indications, contraindications, warnings, and requirements for use of ultrasound contrast agents in cardiovascular applications have occurred during the preparation of this paper, underscoring how important it is that clinicians using contrast agents always be cognizant of the balance between potential safety concerns and clinical benefit.

At the time of this publication's writing, there were no approved contrast agents for perfusion imaging. Contrast enhancement is routinely noted in the myocardium during contrast rest and stress imaging because the same low-MI, real-time, multipulse ultrasound techniques used for detection of myocardial perfusion are also used for optimal LVO, endocardial visualization, and regional wall-motion abnormality detection. Moreover, a growing number of investigative reports have confirmed the utility of off-label use of contrast agents for simultaneous assessment of myocardial perfusion and function in the diagnosis of CAD.[7,97,128-132] The ASE is further evaluating this application, and subsequent reports are anticipated.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.echo.2008.09.009.

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APPENDIX A

Methodology for Evaluation of Cardiac Masses Using Contrast Echocardiography

Contrast agent. Contrast agent is administered with a slow IV push or continuous IV infusion, adjusted for optimal enhancement of the mass.

Equipment settings. Masses are imaged using grayscale (or chroma) power modulation in either real time or a triggered mode with a low MI (0.1-0.2). The gain and compression settings are optimized for visualization of perfusion of the mass (typically 40%-80%). The focus is set at the level of the mass.

Imaging protocol. An ultrasound impulse of high MI (1.0-1.6) is transmitted for 4 to 10 frames, as needed, to destroy microbubbles within the mass. This step prevents the recording of false-positive perfusion due to a saturation artifact secondary to high gain settings. Perfusion of the mass can then be confirmed by assessing gradual contrast replenishment of the mass after the high-MI impulse (Supplementary Figure 5 and Supplementary Movies 6 and7).

Data from Powers et al.[12]

APPENDIX B

Methodology for Contrast Echocardiography–Guided Alcohol Septal Ablation for Hypertrophic Cardiomyopathy

1. The guiding catheter is engaged in the left main coronary artery.
2. A small (9-10 × 1.5-3 mm) balloon catheter is advanced over a guidewire into the first major septal perforator artery.
3. Transthoracic echocardiographic imaging is performed during the procedure to monitor ventricular function and measure LV outflow tract gradient.
4. Before the injection of ethanol, myocardial opacification is achieved by injecting an echocardiographic contrast agent through the balloon lumen to delineate the culprit septal segments.
5. After the identification of the target septal artery with MCE, 1 to 3 cm^3 of ethanol is injected and left in place for 5 minutes.

Several contrast agents for MCE have been used, including Albunex (no longer available), Optison (GE Healthcare), and Levovist (Bayer Schering Pharma AG, Berlin, Germany). Optison should be diluted with saline, and catheter flushing is avoided to minimize LV cavity opacification. Alternatively, it is possible to identify a myocardial blush with transthoracic imaging after injecting the radiographic contrast agent. However, the mere injection of radiographic contrast agent is associated with less brightness (in comparison with echocardiographic contrast agents), which can be enhanced with some agitation. In and of itself, MCE with intracoronary echocardiographic contrast agents has not been associated with chest pain, abnormal myocardial function, or dysrhythmia.

APPENDIX C

Reimbursement Primer for Contrast Echocardiography

Payment rules often differ from plan to plan, but Medicare fee-for-service reimbursement policy provides a frame of reference. Reimbursement varies with site of service (Table C1). For echocardiographic studies in an outpatient setting, including physicians' offices and hospital outpatient facilities, Medicare reimburses the cost of the contrast agent. For hospital inpatients, reimbursement is based on a single payment for the entire hospitalization, regardless of actual costs; the use of a contrast agent generates no additional payment.

Table C1 Medicare reimbursement systems and sites of service

Payment system	Methodology	Site of service
Medicare fee schedule	Resource-based relative value scale	Physician office
Hospital outpatient prospective payment system	Ambulatory payment classification	Hospital outpatient
Hospital inpatient prospective payment system	Diagnosis-related group	Hospital inpatient

Table C2 2008 Current Procedural Terminology (CPT) and Healthcare Current Procedure Coding System (HCPCS) codes for echocardiographic services and echocardiography contrast agents*

CPT/HCPCS code	Abbreviated descriptor
93307	Echocardiography, transthoracic, two-dimensional (2D) with or without M-mode, complete
93308	Echocardiography, transthoracic, real-time (2D) with or without M-mode, limited
93320	Doppler echocardiography, spectral, complete
93321	Doppler echocardiography, spectral, limited
93325	Doppler echocardiography, color flow-velocity mapping
93350	Echocardiography, transthoracic, at rest and with stress (treadmill, bicycle, or pharmacologic stress)
93015	Cardiovascular stress testing, including continuous electrocardiographic monitoring, with physician supervision, interpretation, and report
C8921†	Transthoracic echocardiography with contrast enhancement for congenital cardiac anomalies, complete
C8922	Transthoracic echocardiography with contrast enhancement for congenital cardiac anomalies, follow-up or limited study
C8923	Transthoracic echocardiography with contrast enhancement, real-time with image documentation (2D) with or without M-mode recording, complete
C8924	Transthoracic echocardiography with contrast enhancement, real-time with image documentation (2D) with or without M-mode recording, follow-up or limited study
C8925	Transesophageal echocardiography with contrast enhancement, real-time with image documentation (2D) with or without M-mode recording, including probe placement, image acquisition, interpretation, and report
C8926	Transesophageal echocardiography with contrast enhancement for congenital cardiac anomalies, including probe placement, image acquisition, interpretation, and report
C8927	Transesophageal echocardiography with contrast enhancement for monitoring purposes, including probe placement, real-time 2D image acquisition and interpretation leading to ongoing (continuous) assessment of (dynamically changing) cardiac pumping function and to therapeutic measures on an immediate-time basis
C8928	Transthoracic echocardiography with contrast, real-time with image documentation (2D), with or without M-mode recording, during rest and cardiovascular stress test using treadmill, bicycle exercise, and/or pharmacologically induced stress, with interpretation and report
36000	Introduction of intravenous needle or intracatheter
90870	Intravenous infusion for diagnosis or therapy (administered by physician or under direct physician supervision)
90774	Intravenous injection, therapeutic, prophylactic, or diagnostic
Q9956	Octaflouropropane microspheres (Optison§)
Q9957	Perflutren lipid microspheres (Definity‖)

*CPT copyright 2007 American Medical Association (AMA). All rights reserved. CPT is a registered trademark of the AMA. Applicable Federal Acquisition Regulations System and Defense Federal Acquisition Regulation Supplement restrictions apply to government use. Fee schedules, relative value units, conversion factors, and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein.

†C codes were developed by Medicare and are only reported by hospitals for outpatient procedures.

§GE Healthcare (Princeton, NJ).

‖Lantheus Medical Imaging (North Billerica, MA).

Adapted from Am J Cardiol[133] and American Medical Association.[134]

Necessary documentation. A proper claim must include documentation about (1) the procedure performed, (2) the contrast agent used, and (3) the medical necessity (indication) for the procedure. Most medical procedures, including echocardiography, are coded with the Current Procedural Terminology (CPT) system. Drugs (including contrast agents) are coded with the Healthcare Common Procedure Coding System (HCPCS). The clinical diagnosis that justifies an echocardiogram is coded with the International Classification of Diseases, Ninth Revision (ICD-9).

Table C2[133,134] lists codes current in 2008 for echocardiography procedures and contrast agents. It is important to note that billing and coding rules differ among insurance companies. The availability of a code does not guarantee reimbursement.

For example, a patient with dyspnea undergoes transthoracic echocardiography in a physician's office, resulting in poor-quality baseline images. Definity is used to improve endocardial border definition and to salvage an otherwise nondiagnostic study. Spectral and color Doppler techniques are used to evaluate for valvular regurgitation and to measure pulmonary artery pressure. Thus, the claim would list codes for the services (93307, 93320, and 93325) and the contrast agent (Q9957). The clinical indication would be coded 786.09, the ICD-9 code for dyspnea. A complete list of ICD-9 codes that justify echocardiography as medically necessary is beyond the scope of the present article. Approved ICD-9 codes for echocardiography procedures vary among different insurance carriers and also with the procedure performed.

In the hospital outpatient setting, the same service would be described for Medicare by using different codes. The claim would list HCPCS code C8923, which describes the transthoracic echocardiographic imaging study combined with contrast enhancement, and would report the number of units used for Definity with code Q9957 and the medical necessity with code 786.09.

At the time of this publication, hospital outpatient payments for echocardiographic contrast media were packaged into the associated procedures by Medicare. Table C2 lists 8 new HCPCS codes for echocardiography with contrast enhancement. Hospitals performing

outpatient echocardiography procedures without contrast enhancement should continue to use the current CPT codes (ie, 93303-93350).

Myocardial perfusion with echocardiography contrast. The FDA still considers the use of echocardiographic contrast enhancement to evaluate myocardial perfusion to be an experimental use. Therefore, reimbursement for myocardial perfusion with echocardiography is not permissible under Medicare rules. After this indication gains approval, the development of new CPT codes is likely. The process is time consuming, and typical requirements for personnel, resources, image acquisition, and physician work will need to be defined so that appropriate reimbursement can be determined.

Future reimbursement issues. The current reimbursement scheme has several shortcomings. Contrast agent reimbursement is based on the average sales price, but some clinics pay higher than average prices. The current payment method does not cover the extra personnel and resource costs involved in establishing IV access, preparing and administering the agent, and recording the additional contrast-enhanced images. IV equipment costs also are not covered. Additional reimbursement seems appropriate, but potential consequences deserve note.

Personnel and supply costs are practice expenses. Medicare rules define practice expenses for a given service as those expenses pertaining to the typical patient. The additional costs of contrast echocardiography are not considered echocardiography practice expenses because contrast is used in fewer than 50% of patients undergoing echocardiography. If practice expenses for contrast administration were added to existing reimbursement, revised payment levels would apply to all echocardiographic studies, even if no contrast were used. This addition might encourage practitioners not to use a contrast agent, because they would be paid for doing so without having to bear the extra expense of the agent.

Interpreting a contrast echocardiographic study involves extra work. The physician must review the baseline images and the contrast-enhanced images and include information about the agent and the relevant findings in the final report. Additional physician reimbursement might appear warranted. However, some payers have suggested that because contrast-enhanced images provide better data, the use of contrast enhancement makes it easier for the interpreting physician to reach a diagnosis, which would justify reduced reimbursement.

Currently, the use of contrast medium for LV border opacification is reimbursable in many circumstances. Not all costs are covered, but in a budget-neutral reimbursement system, major improvements are difficult and take time to accomplish and may affect other reimbursements. The ASE, along with the American College of Cardiology, is working with government agencies and various payers to highlight the importance of appropriate use of echocardiographic contrast agents in select clinical echocardiographic settings and the need for respective coding and reimbursement for these services.

In 2009, modifications and new echocardiographic CPT codes will be introduced that will be applicable to contrast echocardiographic procedures. These changes will be posted on the ASE's Web site (http://www.asecho.org), after the information becomes publicly available.