IMPROVING ECHOCARDIOGRAPHY: A CLEARER VIEW

Clinical Applications of Ultrasonic Contrast Agents in Echocardiography

Author: Sherif F. Nagueh, MD, FACC, FAHA, FASE

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*Clinical Applications of Ultrasonic Contrast Agents in Echocardiography*
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Dr. Sherif F. Nagueh, cardiologist and associate director of the echocardiography laboratory at the Methodist DeBakey Heart & Vascular Center in Houston, is professor of Medicine at Weill Cornell Medical College, and Associate Director of the echocardiography laboratory.

He has special interests in cardiac imaging, and hypertrophic cardiomyopathy. In addition to his clinical practice, Dr. Nagueh pursues an active research agenda, with interests in cardiomyopathy and left ventricular diastolic function.

Dr. Nagueh received his medical degree from Cairo University in Egypt. He completed his residency in internal medicine at Baylor College of Medicine, then completed his fellowship in Cardiology and echocardiography at Baylor College of Medicine. He has passed the certification and recertification examinations in internal medicine, cardiovascular diseases and echocardiography.

Dr. Nagueh is active in the national and international scientific community. He has authored over 100 manuscripts, and 7 book chapters related to cardiac diagnosis, and patient care issues.

He is a fellow of the American College of Cardiology, the American Heart Association and the American Society of Echocardiography (ASE), and serves on the board of directors of ASE and on the Intersocietal Commission for Accreditation of Echocardiography Laboratories (ICAEL). He sits on the editorial boards of several peer-reviewed journals, including Circulation, the Journal of the American College of Cardiology, JACC imaging, Clinical Science, Cardiosource, and the Journal of the American Society of Echocardiography.
Following the program, participants will be able to

1. **Differentiate** between echocardiographic images in patients with and without the use of contrast-enhancing agents and their impact on cardiac assessments

2. **Comprehend** the use of contrast agents for various patient populations and echocardiographic procedures

3. **Consider** the use of contrast agents in light of safety concerns

4. **Evaluate** the impact of use of contrast agents on long-term patient management costs and health outcomes
Evaluating echocardiograms can be difficult, and inconclusive results or inaccurate diagnoses can lead to serious problems for critically ill patients. Use of a contrast agent can greatly enhance the clinician's ability to visualize cardiac structure and assess cardiac function, which can significantly impact patient management.

This monograph examines the ability of contrast echocardiography (CE) to enhance the quality and interpretation of echocardiographic studies in several patient settings and presents current safety concerns and recommendations for agent administration.

AGENTS
The contrast agents in use today are microbubbles of gas, with each bubble surrounded by a thin, permeable shell. Optison (GE-Amersham Health, Princeton, NJ) and Definity (Bristol-Meyers Squibb MI, Inc., Billerica, MS) are approved for use in the United States (Table 1).

Table 1. Echocardiographic Contrast Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mean Bubble Size (range), mm</th>
<th>Gas</th>
<th>Shell Composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optison*</td>
<td>4.7(1-10)</td>
<td>Perfluoropropane</td>
<td>Human albumin</td>
</tr>
<tr>
<td>Definity †</td>
<td>1.5(1-10)</td>
<td>Perfluoropropane</td>
<td>Phospholipid</td>
</tr>
<tr>
<td>SonoVue</td>
<td>2.5(1-10)</td>
<td>Sulfur hexafluoride</td>
<td>Phospholipid</td>
</tr>
<tr>
<td>Levovist</td>
<td>2-3(2-8)</td>
<td>Air</td>
<td>Palmitic acid</td>
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</table>

* FDA - approved December 1997.
† FDA - approved July 2001.
IMPROVING ECHOCARDIOGRAPHY: A CLEARER VIEW

ENHANCEMENT OF ECHOCARDIOGRAPHY QUALITY

Cardiac Function – Interpretability and Assessment Accuracy
For echocardiographers it is crucial to have the best diagnostic tools available when assessing cardiac function. The addition of contrast agents to echocardiography exams gives diagnosticians added confidence to correctly evaluate them and improves diagnostic accuracy and interpretability, as several studies have shown.2–4

- Left ventricular volume
- Left ventricular ejection fraction
- Left ventricular noncompaction
- Myocardial infarction complication
- Aortic stenosis

CE can have a major impact on assessment of these cardiac functions:

To assess the accuracy of CE, Malm et al.2 evaluated how well measurements of left ventricular (LV) volume and ejection fraction (EF) matched up to measurements derived from magnetic resonance imaging (MRI), often considered the gold standard. The investigators found that the measurement differences between CE and MRI were significantly less than the differences between noncontrast echocardiography and MRI (P < .05).

Having confidence in interpretation of measurements is also crucial, and contrast increases confidence. In a prospective trial of 632 hospitalized and critically ill patients, the interpretability of LV volume was evaluated. Before use of contrast, nearly all echocardiograms were categorized as technically difficult to interpret (86.7%) or uninterpretable (11.7%). After use of contrast, only 9.8% were deemed technically difficult to interpret and 0.3% uninterpretable (P < .001) (Fig. 1).
In the same trial investigators examined the impact of CE on EF assessment and found that nearly 17% of clinicians changed their assessment after viewing contrast studies (94.5% of EF changes were increases). EF interpretability also significantly improved: interpretable studies increased from 88.3% to 99.7% (P < .001), and uninterpretable studies dropped from 11.7% to 0.3% (P < .001).3

Interpretability of stress echocardiography studies for diagnosing coronary artery disease (CAD) is equally important. In the 2007 OPTIMIZE trial, clinicians were asked to evaluate dobutamine stress echocardiography (DSE) studies for CAD, before and after contrast. When CAD detection agreement was at low confidence, CE had a significant impact, raising agreement from 36% to 68% (P < .01). The trend continued in medium-confidence studies, but the difference was no longer significant.

ASSESSMENT OF CARDIAC ANATOMY AND EXTRACARDIAC STRUCTURES

CE enhances assessment of normal and abnormal cardiac anatomy and extracardiac structures. Examples of these include the following:

- Endocardial segments (and wall motion)
- LV hypertrophy (Fig. 2)
- Ballooning
- Aneurysms and pseudoaneurysms
- LV apical clots (Fig. 3)
- Intracardiac masses

To evaluate the ability of CE to enhance cardiac segment visualization, Kurt et al.3 examined 632 CE studies in various patient settings. The investigators found that contrast use significantly increased visualization when normal and abnormal segments were grouped together (11.6 segments before, 16.8 after) and when abnormal segments were evaluated alone (2.5 before, 3.9 after). CE enhanced visualization in all patient settings; however, its greatest effect was seen in critically ill patients in intensive care units (ICUs).5

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1 At least ±10%.
Critically ill patients, in whom accurate and timely cardiac assessment is crucial, present a unique problem for echocardiography. Because they are bedridden, intubated, catheterized, and “wired” to machines, often they are not candidates for invasive transesophageal echocardiography (TEE) or for transport to the nuclear imaging department for MRI. In these cases, CE can provide clinicians with the same visualization confidence they would have using TEE.

Yong et al. evaluated this by comparing visualization capabilities of 4 echocardiography modalities: noncontrast transthoracic echocardiography (TTE), noncontrast harmonic TTE, contrast harmonic TTE, and TEE. The cardiac segment studies graded excellent or adequate were evaluated. The differences between the 3 noninvasive studies were significant (p < .001), whereas the difference between contrast harmonic TTE and TEE was not. Regional wall motion interpretability also increased, from 68% for noncontrast TTE to 92% for contrast harmonic TTE and 96% for TEE (Fig. 4).

Contrast can also enhance cardiac structure visualization in settings where patients are not critically ill, e.g., the outpatient stress echocardiography setting. In a DSE study of 101 patients, CE increased the percentage of cardiac segments with adequate or excellent visualization; the percentage rose from 72% to 95% at rest and from 67% to 96% at maximal stress (p < 0.001). Interpreter confidence in what was seen also increased dramatically, with 36% reporting high confidence before use of contrast and 74% after use of contrast (p < .001).

EFFECTS ON PATIENT MANAGEMENT

CE changes how clinicians treat and further diagnose their patients, e.g., medication regimens are altered, or additional diagnostic procedures are canceled. CE also affects associated costs and utilization of resources.

Kurt et al. asked clinicians, after having analyzed a patient’s LV function without contrast, to mock-prescribe (but not administer) clinically necessary medication. A CE exam was then performed on the same patient, and clinicians were again asked to prescribe medication based on the new exam. In a statistically significant percentage of cases (10.6%), medication regimens were modified. This included starting or stopping anticoagulation after confirmation or exclusion of a thrombus (Fig. 3) and adding or discontinuing hemodynamically active drugs. Regimen changes were most notable in surgical ICU patients, occurring 25.5% of the time.
there were 31.3% fewer procedures prescribed for inpatients, 33.4% fewer for medical ICU patients, and 54.9% fewer for surgical ICU patients.\textsuperscript{3}

Techniques recommended for optimal CE outcomes

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Set the ultrasound device’s mechanical index to 0.15-0.3</td>
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<tr>
<td>Optimize time gain compensation and gain</td>
</tr>
<tr>
<td>Minimize near-field gain</td>
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<tr>
<td>Draw the agent after vial venting, no air</td>
</tr>
<tr>
<td>Inject a bolus (0.5-1 mL/s) or a diluted bolus of the agent</td>
</tr>
<tr>
<td>Slowly flush the bolus with saline (2-3 mL over 3-5 seconds)</td>
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<tr>
<td>When contrast appears in the right ventricle, stop the flush</td>
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<tr>
<td>Use additional doses as needed</td>
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Patient monitoring warnings\textsuperscript{6}

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<td>During and for at least 30 minutes after administration of contrast agents, patients with pulmonary hypertension or unstable cardiopulmonary conditions should be monitored with vital sign measurements, electrocardiography, and cutaneous oxygen saturation.</td>
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<tr>
<td>Resuscitation equipment and trained personnel should always be readily available during the administration and monitoring period.</td>
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SAFETY

In October 2007, as a result of 4 reported deaths temporally associated with echocardiographic contrast agents, the FDA mandated that Definity and Optison add several new contraindications to their labels as “black box” warnings. (The original contraindications were right-to-left, bidirectional, or transient right-to-left cardiac shunts and hypersensitivity to perflutren.)

\textsuperscript{1} Worsening or clinically unstable congestive heart failure, acute myocardial infarction, or acute coronary syndromes; serious ventricular arrhythmias or high risk of arrhythmias due to prolongation of the QT interval; respiratory failure; and severe emphysema, pulmonary emboli, or other conditions that cause pulmonary hypertension.
In light of this mandate, and in an attempt to understand the cause(s) of the deaths, researchers retroactively analyzed the safety of these contrast agents.

One such retrospective study reviewed 12,475 noncontrast and 6,196 contrast studies performed from 2005 to 2007. No significant difference in mortality (0.37% vs 0.42%, respectively; P < .6) was observed within 24 hours even though patients who underwent contrast studies were sicker, with higher baseline clinical acuities and more significant comorbidities.

Another study, a review of 5,069 stress echocardiography exams conducted over an 8-year period, showed that CE patients experienced more chest pain (11% vs 8%), back pain (0.6% vs 0.05%), and premature ventricular contractions (PVC) (odds ratio, 1.42) than noncontrast patients. However, no ventricular tachycardias, ventricular fibrillations, cardiac arrests, or deaths occurred in either group. When investigators analyzed the groups’ arrhythmia rates and the 1 myocardial infarction and 1 anaphylactic reaction in the CE group, no statistically significant difference between groups was found (p = 0.8, p = 0.51, p = 0.51, respectively). In summary, adverse event rates were similar even though the CE patients were older and had significantly depressed baseline EFs (<50%, 14% vs 11%; P < .001).

Finally, a study of nearly 19,000 stress echocardiography exams, spanning from 1999 to 2007, revealed death and myocardial infarction rates of 0.34% and 0.68%, respectively, within 30 days of contrast administration. These rates were not significantly different from those of a temporally matched, noncontrast cohort of 16,000, whose rates were 0.39% and 0.46%, respectively.

These recent studies, and the previously established safety of echocardiography contrast agents, demonstrate CE to be as safe as noncontrast studies.

Eight months after the FDA mandated the new contraindications, it relaxed its stance and allowed them to be listed as warnings.
CE can enhance the quality and interpretability of echocardiographic studies in several patient settings, most notably the ICU, where other modalities for cardiac assessment are limited. CE can also positively impact patient care through more appropriate prescribing of medication and by reducing the need for additional diagnostic tests. Finally, the safety profile of CE, recently addressed by the FDA, has been shown to be similar to that of noncontrast echocardiography by several large retrospective studies. Used in the correct setting and administered as recommended, CE can have a major beneficial impact on patient management.

No PVCs converted into more serious arrhythmias. The investigators suggested that the higher PVC rate was a result of more contrast patients receiving DSEs and dobutamine’s ventricular ectopy-inducing property.
For left ventricular volume assessment in several patient settings, nearly all precontrast exams were technically difficult to interpret or uninterpretable. After contrast, only 10% remained technically difficult to interpret or uninterpretable. Inpt indicates inpatient; MICU, medical intensive care unit; and SICU, surgical intensive care unit. Reprinted with permission from Kurt M, et al. J Am Coll Cardiol. 2009;53(9):802-810. © 2009, American College of Cardiology. All rights reserved.
Contrast for Apical HCM

The contrast-enhanced image (right) delineates blood flow (bright yellow) and hypertrophic cardiac tissue (upper, circular dark area). HCM indicates hypertrophic cardiomyopathy.
Absence of Perfusion in an Apical Clot

The contrast-enhanced image (right) delineates blood flow (bright yellow) and a thrombus (upper, circular dark area).
Visualization capabilities of 4 echocardiology modalities: noncontrast transthoracic echocardiography (TTE; fundamental imaging), noncontrast harmonic TTE, contrast harmonic TTE, and transesophageal echocardiography (TEE). In cardiac segment studies graded excellent or adequate, differences between TTE studies were significant (P < .001), but the difference between contrast harmonic TTE and TEE was not. In wall motion studies, interpretability markedly increased, from 68% for noncontrast TTE to 92% for contrast harmonic TTE. ICU indicates intensive care unit. Reprinted with permission from Yong Y, et al. Am J Cardiol. 2002;89(6):711-718. ©2002, Excerpta Medica, Inc. All rights reserved.
REFERENCES


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Scale: 1 = poor  2 = fair  3 = good  4 = very good  5 = excellent

Overall program rating 1 2 3 4 5
Relevance of program to your practice 1 2 3 4 5
Effectiveness of brief 1 2 3 4 5
The educational level of this brief was 1 2 3 4 5
The presentation was objective, balanced and free of commercial bias? Yes No

Learning Objectives Review: Was each learning objective met?

Differentiate between echocardiography images in patients with and without the use of contrast enhancing agents and their impact on cardiac assessments Yes No

Comprehend the utilization of contrast agents for various patient populations, and echocardiography procedures Yes No

Consider the use of contrast agents in light of safety concerns Yes No

Evaluate the impact of use of contrast agents on long-term patient management costs and health outcome Yes No

Based on information you gained in this activity, do you plan to make any changes in your patient care activity? Yes No N/A

If yes, what changes?
IMPROVING ECHOCARDIOGRAPHY: A CLEARER VIEW

Please indicate your answers on the continuing education form provided on page 23

1. The two FDA-approved contrast agents, Optison and Definity, are microbubbles with different shells, but share the same interior gas, which is:
   a) Carbon dioxide
   b) Perfluoropropane
   c) Air
   d) Sulfurhexachloride

2. The use of contrast agents in echocardiography:
   a) Improves assessment of cardiac function
   b) Improves patient management
   c) Lessens the patient burden in emergency departments
   d) a and b
   e) a, b and c

3. Contrast use can increase the diagnostic yield in which of the following conditions?
   a) Myocardial infarction
   b) LV hypertrophy
   c) Coronary artery disease
   d) Apical clot
   e) All of the above

4. Use of contrast allows for more reliable:
   a) LV volume assessment
   b) LV EF assessment
   c) Endocardial segment visualization
   d) b and c
   e) a, b and c

Clinical Applications of Ultrasonic Contrast Agents in Echocardiography
5. Which list arranges echocardiography modalities from least to most efficacious?
   a) Non-contrast harmonic TTE, contrast harmonic TTE, non-contrast TTE
   b) Non-contrast TTE, non-contrast harmonic TTE, contrast harmonic TTE
   c) Non-contrast TTE, contrast harmonic TTE, non-contrast harmonic TTE
   d) Contrast harmonic TTE, non-contrast harmonic TTE, non-contrast TTE

6. Which is true regarding contrast administration during stress echocardiography?
   a) It should not be used during maximal stress
   b) It should not be used with pharmacologic stress studies
   c) It can increase interpretation agreement
   d) a and b
   e) all the above

7. Contrast use can most reduce downstream imaging procedures in which setting?
   a) Outpatient
   b) Medical ICU
   c) Surgical ICU
   d) Inpatient wards

8. What is required for patient monitoring during administration of contrast agents?
   a) Patients with pulmonary hypertension should be monitored with cutaneous oxygen saturation and electrocardiography for the first 30 minutes post procedure.
   b) Resuscitation equipment and trained personnel should be available during the administration and monitoring period.
   c) Patients should be admitted to the critical care unit for monitoring.
   d) a and b
9. Which statements are true regarding contrast agent safety?
   a) The October 2007 FDA “black box” warning mandate was a result of 4 deaths temporally associated with echocardiographic contrast agents.
   b) Contrast echocardiography has a slightly increased mortality rate compared to non-contrast studies.
   c) Right-to-left cardiac shunts are current contraindications for contrast use.
   d) a and c
   e) All of the above

10. The imaging modality with the best feasibility-efficaciousness profile for assessing cardiac function in critically ill patients, i.e., ICU patients, is:
    a) TEE
    b) MRI
    c) Contrast echocardiography
    d) Non-contrast echocardiography
    e) none of the above
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(Please circle the correct answer)

1. a b c d
2. a b c d
3. a b c d
4. a b c d
5. a b c d
6. a b c d
7. a b c d
8. a b c d
9. a b c d
10. a b c d