Presentation materials

• Steven B. Feinstein, MD, FACC FESC
• Professor of Medicine/Cardiology
• Rush University Medical Center
  • Chicago, Illinois

• Collaborator
• Michael Main, MD, FACC. FASE
  • St. Luke's Medical Center
    • Kansas City, Kansas
Are We Doing Too Many Inpatient Echocardiograms?  
The Answer From Big Data May Surprise You!*  

Christine L. Jellis, MD, PhD, Brian P. Griffin, MD

At this time, therefore, the use of such alternative diagnostic tools cannot replace the comprehensive evaluation provided by a complete TTE including 2D imaging, comprehensive Doppler interrogation and volumetric analysis. In many of these challenging cases, the further use of echo contrast, 3D imaging and even transesophageal echocardiography by experienced operators can have a significant impact on diagnosis and management (7–9).
U.S. Hospital Use of Echocardiography
Insights From the Nationwide Inpatient Sample

Alexander Papolos, MD, Jagat Narula, MD, PhD, Chirag Bavishi, MD, MPH, Farooq A. Chaudhry, MD, Partho P. Sengupta, MD, DM

**Figure 2** Sample Rates of Diagnostic Cardiac Catheterization and Echo by Admission Diagnosis

AMI = acute myocardial infarction; CAD = coronary artery disease; Cath = cardiac catheterization; CHF = congestive heart failure; Echo = echocardiography.
CONCLUSIONS

Echo use was associated with decreased odds of hospital mortality among 5 of the leading 6 admission diagnoses for which echo was most commonly reported in the 2010 NIS database. These 5 diagnoses account for approximately 3.7 million national hospitalizations annually; however, in 2010 the NIS database reported echo use in only 8% of cases. Because patient selection and appropriate echo use are key to cost efficiency, this study suggests that echo may be underused during critical cardiovascular hospitalizations, most notably in the treatment of AMI.
Limiting use of ionizing radiation for diagnostic medical imaging

Circulation 2009: A Science Advisory From the American Heart Association Committee on Cardiac Imaging of the Council on Clinical Cardiology and Committee on Cardiovascular Imaging and Intervention of the Council on Cardiovascular Radiology and Intervention...

• “As a result of the changes in use of imaging procedures that rely on ionizing radiation, the collective dose has increased by over 700%, and the annual per-capita dose by almost 600% in recent years.”

• “Physician education should emphasize that cardiac imaging studies that expose patients to ionizing radiation should be ordered only after thoughtful consideration of the potential benefit to the patient and in keeping with established appropriateness criteria.”
Radiation post-treatment of MI/risks

Cardiac Imaging May Raise Cancer Risk

Study Shows Potential Long-Term Risks of Scans Performed After Heart Attacks
By Bill Hendrick WebMD Health News

Feb. 7, 2011  Louise Pilote, MD, PhD, MPH, of McGill University,

They say doctors “should at least consider putting into place a system of prospectively documenting the imaging tests and procedures that each patient undergoes and estimating his or her cumulative exposure to low-dose ionizing radiation.”
Growth in non-invasive imaging
Acoustic microspheres
diagnostic and therapeutic vehicles

Capillary transit 1982
400 frames/sec

In vitro imaging 2005
20M/frames/sec
<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Name</th>
<th>Type</th>
<th>Development Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acusphere</td>
<td></td>
<td>Polymer/perfluorocarbon</td>
<td>Clinical development</td>
</tr>
<tr>
<td>Alliance/Schering</td>
<td>Imavist</td>
<td>Encapsulated perfluorocarbon</td>
<td>Clinical development</td>
</tr>
<tr>
<td>Andaris</td>
<td>Quantison</td>
<td>Albumin/low-solubility gas</td>
<td>Clinical development</td>
</tr>
<tr>
<td>Bracco</td>
<td>SonoVue</td>
<td>Lipid/sulfur hexafluoride</td>
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</tr>
<tr>
<td>Byk-Gulden</td>
<td>BY963</td>
<td>Lipid/air (BY963)</td>
<td>Clinical development</td>
</tr>
<tr>
<td>Cavcon</td>
<td>Filmix</td>
<td>Lipid/air</td>
<td>Preclinical development</td>
</tr>
<tr>
<td>Lantheus Medical Imaging</td>
<td>Definity</td>
<td>Pentane/Octafluoropropane</td>
<td>Approved for clinical use</td>
</tr>
<tr>
<td>GE Healthcare</td>
<td>Optison</td>
<td>Sonicated albumin/octafluoropropane</td>
<td>Approved for clinical use</td>
</tr>
<tr>
<td>GE Healthcare</td>
<td>Sonazoid</td>
<td>Lipid/perfluorocarbon</td>
<td>Approved for clinical use</td>
</tr>
<tr>
<td>Point Biomedical</td>
<td>Bisphere</td>
<td>Perfluorocarbon/polymer bilayer</td>
<td>Clinical development</td>
</tr>
<tr>
<td>Porter MD/University of Nebraska</td>
<td>PESDA</td>
<td>Sonicated albumin/perfluoropropane</td>
<td>Not commercially available</td>
</tr>
<tr>
<td>Schering</td>
<td>Echovist</td>
<td>Lipid/air</td>
<td>Approved for clinical use</td>
</tr>
<tr>
<td>Schering</td>
<td>Levovist</td>
<td>Lipid/air</td>
<td>Approved for clinical use</td>
</tr>
<tr>
<td>Schering</td>
<td>Sonavist</td>
<td>Polymer/air</td>
<td>Clinical development</td>
</tr>
<tr>
<td>Sonus</td>
<td>Echogen</td>
<td>Surfactant/perfluorocarbon</td>
<td>Withdrawn from development</td>
</tr>
</tbody>
</table>
Diagnostic and Therapeutic Uses of CEUS

• Reduces risk
  – Reduces redundant downstream tests
  – No ionizing radiation or dye
  – No nephrotoxicity

• More accurate and reliable than ultrasound w/o contrast

• Reduces healthcare costs
  – Reduces downstream testing
  – Lower equipment costs

• Changes therapy and saves lives

• International acceptance in cardiac and non-cardiac imaging – South America, Europe, Canada, and Asia
Clinical value of CEUS
Enhanced visualization of cardiac chambers
Endocardial Border Delineation Improved With Contrast Enhancement

pre contrast                       post-contrast
Contiguous Segment Visualization Improved With Contrast Enhancement

pre contrast                              post-contrast
CEUS: Use in critically ill patients

Case #1 CR

60 year old woman in the SICU. Post CABG, hypotensive and tachycardiac. Management: diuretics and sympathomimetics.
**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.

“ASE Consensus Statement on the Clinical Applications of Ultrasonic Contrast Agents in Echocardiography, 2008”
ASE Recommended Applications for Ultrasound Contrast Use

In difficult-to-image patients presenting for rest echocardiography with reduced image quality

- To enable improved endocardial visualization and assessment of LV structure and function when >2 contiguous segments are not seen on noncontrast images
- To reduce variability and increase accuracy measurements by 2D echo
- To increase the confidence of the interpreting physician

Suboptimal Imaging Fails to Provide Critical Information for Clinical Decision Making

• Implantable Cardioverter Defibrillators
• Biventricular Pacemakers
• Anthracycline Chemotherapy
• Trastuzumab Chemotherapy
• Epleronone Post-MI
Suboptimal Images: Assessing Left Ventricular Remodeling
Contrast Improves Suboptimal Images: Assessing Left Ventricular Remodeling

Nayyar S et al. Am J Cardiol 2006;98:1110-4
Analysis of Regional Left Ventricular Function by Cineventriculography, Cardiac Magnetic Resonance Imaging, and Unenhanced and Contrast-Enhanced Echocardiography
A Multicenter Comparison of Methods

Rainer Hoffmann, MD,* Stephan von Bardeleben, MD,† Jaroslaw D. Kasprzak, MD,‡ Adrian C. Borges, MD,§ Folkert ten Cate, MD,¶ Christian Fischke, MD, FACC,‖ Stephane Lafitte, MD,# Nidal Al-Saadi, MD,** Stefanie Kuntz-Hehner, MD,†† Georg Horstick, MD,‡ Christian Greis,‡‡ Marc Engelhardt, MD, §§ Jean Louis Vanoverschelde, MD, FACC,|| Harald Becher, MD¶¶

• **Question:** Which technique is best for detection of left ventricular regional wall motion abnormalities (left ventriculography, unenhanced echocardiography, contrast enhanced echocardiography, cardiac MRI)

• **Patient Population:** 100 patients referred for coronary angiography (56 patients underwent all 4 techniques)

Methods: Patients underwent harmonic imaging without contrast, harmonic imaging with contrast, left ventriculography, cardiac MRI
Methods

Consensus expert panel defined presence or absence of regional wall motion abnormality based on clinical data and results of all image reads.

Hoffman et al. J Am Coll Cardiol 2006;47:121-8
Regional Wall Motion Assessment by 4 Imaging Modalities

<table>
<thead>
<tr>
<th></th>
<th>a4CV enddiastolic</th>
<th>enddiastolic</th>
<th>a2CV enddiastolic</th>
<th>enddiastolic</th>
<th>a3CV enddiastolic</th>
<th>enddiastolic</th>
</tr>
</thead>
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<tr>
<td>UE</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>CE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CINE</td>
<td>LAO</td>
<td>BiPlane</td>
<td>RAO</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hoffman et al. J Am Coll Cardiol 2006;47:121-8
# Diagnostic Performance of the 4 Imaging Modalities

<table>
<thead>
<tr>
<th></th>
<th>Echo Unenhanced</th>
<th>Echo Contrast Enhanced</th>
<th>Cineventriculography</th>
<th>cMRI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All patients</strong></td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>56</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>85.7%</td>
<td>90.2%</td>
<td>86.5%</td>
<td>90.8%</td>
</tr>
<tr>
<td>Specificity</td>
<td>77.3%</td>
<td>81.3%</td>
<td>75.0%</td>
<td>74.4%</td>
</tr>
<tr>
<td>Accuracy</td>
<td>82.9%</td>
<td>87.2%</td>
<td>82.8%</td>
<td>84.9%</td>
</tr>
<tr>
<td><strong>Only cMRI patients</strong></td>
<td>56</td>
<td>56</td>
<td>56</td>
<td>56</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>83.3%</td>
<td><strong>90.7%</strong></td>
<td>84.1%</td>
<td>90.8%</td>
</tr>
<tr>
<td>Specificity</td>
<td>73.0%</td>
<td>83.8%</td>
<td>69.4%</td>
<td>74.4%</td>
</tr>
<tr>
<td>Accuracy</td>
<td>79.5%</td>
<td><strong>88.2%</strong></td>
<td>78.7%</td>
<td>84.9%</td>
</tr>
</tbody>
</table>

*p = 0.018 vs. echo unenhanced; p = 0.018 vs. cineventriculography. Abbreviations as in Table 2.
To confirm or exclude the echocardiographic diagnosis of the following LV structural abnormalities, when nonenhanced images are suboptimal for definitive diagnosis

- Apical variant of hypertrophic cardiomyopathy
- Ventricular noncompaction
- Apical thrombus
- Complications of myocardial infarction, such as LV aneurysm, pseudoaneurysm, and myocardial rupture
IAC Standards For Contrast

Contrast is indicated for use when two contiguous segments are not visualized as it provides greater accuracy in determining left ventricular function:

A) If contrast is used, there must be a written policy for the use of contrast agents

B) If contrast is not able to be used there must be a policy for alternative imaging

C) Contrast should be used in the presence of poor endocardial border definition for quantification of chamber dimensions, volumes, ejection fraction and assessment of regional wall motion

D) Poor endocardial border definition is defined as the inability to detect two or more contiguous segments in any three of the apical views

E) Contrast should also be used to assess conditions such as hypertrophic cardiomyopathy or when left ventricular thrombus is suspected
Prospective analysis:
Impact of Contrast Echocardiography on Evaluation of Ventricular Function and Clinical Management in a Large Prospective Cohort

Mustafa Kurt, MD, et al.
Department of Cardiology, The Methodist Hospital

J Am Coll Cardiol, 2009; 53:802-810
(Published online 11 February 2009).
Impact of Contrast Echocardiography on Evaluation of Ventricular Function and Clinical Management in a Large Prospective Cohort

• Question: What is the impact of ultrasound contrast on patient management?

• Methods: 632 consecutive patients underwent both baseline and contrast enhanced examinations

Total Impact of CEUAS on Patient Management


$120 per patient savings
CEUS: Improved clinical care/management

- Un-interpretable studies decreased from 11.7% to 0.3% and technically difficult studies decreased from 86.7% to 9.8% ($p = 0.0001$)

- Therapeutic decisions were changed 10.4%

- Additional procedures avoided; therapy changed 35.6% of patients and the highest impact of the use of ultrasound contrast was observed in the sickest patient base, those housed in the intensive care units.
LV thrombus was suspected in 35 patients; definite in 3 patients before CEUS. Post CEUS only 1 patient had a suspected thrombus, and 5 (new) additional patients with thrombus were identified (p = 0.0001)

CEUS resulted in a cost–benefit analysis of significant savings @ $122/patient

The appropriate use of contrast ultrasound improved endocardial visualization, positively affected diagnostic efficiency, resource utilization, and, critically, resulted in changes in patient management
Impact of Contrast Echocardiography on Evaluation of Ventricular Function and Clinical Management in a Large Prospective Cohort

<table>
<thead>
<tr>
<th>Clinical Assessment</th>
<th>Before Contrast</th>
<th>After Contrast</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspected Thrombus</td>
<td>35</td>
<td>1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Definite Thrombus</td>
<td>3</td>
<td>0</td>
<td>n/a</td>
</tr>
</tbody>
</table>

*In addition, 5 previously undetected thrombi noted with contrast*

Kurt M et al. J Am Coll Cardiol 2009;53:802-810
Conclusions

• Ultrasound contrast agents have a proven safety profile
• There is an approximate 1: 10,000 risk of anaphylactoid reaction; labs should be prepared with allergy kits, including auto-injectable epinephrine
• Effective use of contrast requires clinical and operational champions within the lab
• UCA use may alter outcomes and reduce cost in ambulatory and hospitalized patients with baseline technically difficult studies
Acute Mortality in Hospitalized Patients Undergoing Echocardiography With and Without an Ultrasound Contrast Agent

Results in 18,671 Consecutive Studies

Lisa L. Kusnetzky, BA, Adnan Khalid, MD, Tayeb M. Khumri, MD, Tabitha G. Moe, MD, Philip G. Jones, MS, Michael L. Main, MD, FACC

Kansas City, Missouri

Objectives
We sought to define acute mortality in hospitalized patients undergoing clinically indicated echocardiography with and without use of an ultrasound contrast agent.

Background
The U.S. Food and Drug Administration recently issued a boxed warning and new contraindications for the perflutren-containing ultrasound contrast agents following postmarketing reports of 4 patient deaths that were temporally related to Definity (Bristol-Myers Squibb Medical Imaging, Billerica, Massachusetts) administration. To appreciate the incremental risk of any medical procedure, the ambient risk of untoward outcome in the population in question must first be defined. There are no published data on short-term major adverse cardiac events in hospitalized patients undergoing echocardiography, either with or without administration of an ultrasound contrast agent.

Methods
A retrospective analysis of hospitalized patients undergoing clinically indicated echocardiography between January 2005 and October 2007, within Saint Luke’s Health System, Kansas City, Missouri, was performed. Studies were separated into 2 groups, those performed without contrast enhancement (n = 12,475) and those performed with Definity (n = 6,196). Vital status within 24 h of the echocardiographic study was available for all patients using a combination of the Social Security Death Master File and Saint Luke’s Health System medical records. Incidence of death within 24 h was compared by chi-square test between Definity and unenhanced procedures.

Results
Of the 18,671 patient events, 72 patients died within 24 h. Of those that underwent unenhanced echocardiography, 46 died within 24 h (0.37%). Of patients receiving Definity during the echocardiogram, 26 died within 24 h (0.42%). There was no statistical difference between these 2 groups (p = 0.60). No patient died within 1 h of the echocardiographic study. In a random sampling from the unenhanced (n = 201) and Definity groups (n = 202), patients who underwent Definity-enhanced echocardiography exhibited higher clinical acuity, and more significant comorbidities.

Conclusions
Approximately 0.4% of hospitalized patients die within 24 h of echocardiography. There is no increased mortality risk associated with Definity-enhanced examinations, despite evidence for higher clinical acuity and more comorbid conditions in patients undergoing contrast studies.

18,671 patients
- 12,475 unenhanced
- 6,196 DEFINTITY®

In-patient echocardiography between January 2005 and October 2007

Vital status at 24 hours available for all patients
Results

Table 1: Characteristics of Patients Undergoing Echocardiography With and Without Contrast Enhancement

<table>
<thead>
<tr>
<th></th>
<th>Echocardiography With Contrast (n = 202)</th>
<th>Unenhanced Echocardiography (n = 201)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>66.1 ± 15.0</td>
<td>64.2 ± 18.3</td>
<td>0.254</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>72 (35.6%)</td>
<td>117 (58.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male</td>
<td>130 (64.4%)</td>
<td>84 (41.8%)</td>
<td></td>
</tr>
<tr>
<td>Hospital length of stay</td>
<td></td>
<td></td>
<td>0.181</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>9.6 ± 25.7</td>
<td>7.1 ± 8.9</td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>5.0 (3.0–8.0)</td>
<td>4.0 (2.0–9.0)</td>
<td></td>
</tr>
<tr>
<td>ICU (days)</td>
<td></td>
<td></td>
<td>0.007</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>2.9 ± 9.5</td>
<td>1.0 ± 2.4</td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>0.0 (0.0–3.0)</td>
<td>0.0 (0.0–1.0)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>73 (36.3%)</td>
<td>37 (18.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>173 (86.1%)</td>
<td>118 (58.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td></td>
<td></td>
<td>0.107</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>1.6 ± 1.3</td>
<td>1.4 ± 1.2</td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>1.2 (0.9–1.6)</td>
<td>1.1 (0.9–1.4)</td>
<td></td>
</tr>
<tr>
<td>Chronic obstructive lung disease</td>
<td>48 (23.9%)</td>
<td>22 (10.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>143 (71.1%)</td>
<td>64 (31.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke</td>
<td>37 (18.4%)</td>
<td>31 (15.4%)</td>
<td>0.425</td>
</tr>
<tr>
<td>Left ventricular ejection fraction</td>
<td>48.3 ± 15.8</td>
<td>58.9 ± 12.1</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Continuous variables are reported as mean ± SD and/or median and IQR as appropriate, and were compared using t tests. Categorical variables are reported as frequency and percent and were compared using chi-square tests.

Kusnetzky LL et al. J Am Coll Cardiol 2008;51:1704-5

Conclusion:

- No difference in 24 hour mortality in hospitalized patients undergoing echocardiography with or without contrast administration.
Conclusions: In critically ill, propensity-matched hospitalized patients undergoing echocardiography, use of a UCA is associated with a 28% lower mortality at 48 h in comparison with patients undergoing non-contrast enhanced echocardiography. The results are reassuring given the previous reports suggesting an association between UCAs and increased mortality in critically ill patients.

J Am Coll Cardiol : http://dx.org.10.1016/j.jcmg.2013.08.012
Meta-Analysis of Adverse Cardiovascular Events Associated with Echocardiographic Contrast Agents

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Contrast Events</th>
<th>Total</th>
<th>No Contrast Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
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</thead>
<tbody>
<tr>
<td>Abdelmalek</td>
<td>37</td>
<td>10792</td>
<td>57</td>
<td>15982</td>
<td>20.6%</td>
<td>0.96 [0.84, 1.45]</td>
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</tr>
<tr>
<td>Anantharam</td>
<td>0</td>
<td>1150</td>
<td>0</td>
<td>2554</td>
<td></td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Dolan</td>
<td>37</td>
<td>42408</td>
<td>62</td>
<td>23812</td>
<td>20.7%</td>
<td>0.33 [0.22, 0.50]</td>
<td></td>
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<tr>
<td>Gabriel</td>
<td>10</td>
<td>4786</td>
<td>16</td>
<td>5012</td>
<td>16.0%</td>
<td>0.65 [0.30, 1.44]</td>
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</tr>
<tr>
<td>Kusnetzky</td>
<td>26</td>
<td>12475</td>
<td>46</td>
<td>6196</td>
<td>19.8%</td>
<td>0.28 [0.17, 0.45]</td>
<td></td>
</tr>
<tr>
<td>Main</td>
<td>616</td>
<td>58254</td>
<td>54</td>
<td>4242712</td>
<td>23.0%</td>
<td>0.96 [0.90, 1.06]</td>
<td></td>
</tr>
<tr>
<td>Shaikh</td>
<td>0</td>
<td>2914</td>
<td>0</td>
<td>2155</td>
<td></td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Wei</td>
<td>0</td>
<td>78383</td>
<td>0</td>
<td>780243</td>
<td></td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>726</td>
<td>507866</td>
<td>100.0%</td>
<td>1</td>
<td>0.57 [0.32, 1.01]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 2. Pooled OR for all-cause mortality across studies between patients undergoing and not undergoing contrast imaging.

Khawaja et al. Am J Cardiol 2010;106:742-747
## Table 4
Incidence of allergic/anaphylactic reactions with echocardiography contrast agents

<table>
<thead>
<tr>
<th>Studies</th>
<th>Patients Receiving Contrast Agent (n)</th>
<th>Allergic Reactions (n)</th>
<th>Anaphylactic Reactions (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdelmoneim et al[10]</td>
<td>10,792</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Gabriel et al[13]</td>
<td>4,786</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dolan et al[12]</td>
<td>42,408</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Shaikh et al[15]</td>
<td>2,914</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Main et al[16]</td>
<td>58,254</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Wei et al[17]</td>
<td>78,383</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Kusnetzky et al[14]</td>
<td>12,475</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anantharam et al[11]</td>
<td>1,150</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>110,500 (excluding NA studies)</td>
<td>11 (0.009%)</td>
<td>5 (0.004%)</td>
</tr>
</tbody>
</table>

NA = not applicable.

*Khawaja et al. Am J Cardiol 2010;106:742-747*
FDA Black Box Warning

- October 2007
- Spontaneous healthcare provider reports of several patient deaths and many “severe cardiopulmonary reactions” which occurred in close temporal relationship to UCA injection
- Epidemiologic type study ‘performed by FDA to determine “risk factors” for adverse events with UCA’
Addition of a "Boxed WARNING" to the product label for DEFINITY® and Optison highlighting the risk of "serious cardiopulmonary reactions" within 30 minutes of administration

Multiple new contraindications:
- worsening or clinically unstable heart failure
- acute myocardial infarction or acute coronary syndrome
- serious ventricular arrhythmia or high risk for arrhythmias due to QT prolongation
- respiratory failure
- severe emphysema, pulmonary emboli, or other conditions that cause pulmonary hypertension

Mandated 30 minute monitoring period following contrast administration in all patients
Black Box Warnings

WARNING: Serious Cardiopulmonary Reactions

Serious cardiopulmonary reactions, including fatalities, have occurred during or following perflutren-containing microsphere administration.

- Assess all patients for the presence of any condition that precludes OPTISON administration (see CONTRAINDICATIONS).
- In patients with pulmonary hypertension or unstable cardiopulmonary conditions, monitor vital sign measurements, electrocardiography, and cutaneous oxygen saturation during and for at least 30 minutes after OPTISON administration (see WARNINGS).
- Always have resuscitation equipment and trained personnel readily available.

WARNING: Serious Cardiopulmonary Reactions

Serious cardiopulmonary reactions, including fatalities, have occurred during or following perflutren-containing microsphere administration.

- Assess all patients for the presence of any condition that precludes DEFINITY® administration (see CONTRAINDICATIONS).
- In patients with pulmonary hypertension or unstable cardiopulmonary conditions, monitor vital sign measurements, electrocardiography and cutaneous oxygen saturation during and for at least 30 minutes after DEFINITY® administration (see WARNINGS).
- Always have resuscitation equipment and trained personnel readily available.
# History of Product Label Changes

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>Contraindications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Hypersensitivity to</td>
<td>• Hypersensitivity to</td>
<td>• Hypersensitivity to</td>
<td>• Hypersensitivity to</td>
</tr>
<tr>
<td>octafluoropropane</td>
<td>octafluoropropane</td>
<td>octafluoropropane</td>
<td>octafluoropropane</td>
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<tr>
<td>• Cardiac shunts</td>
<td>• Cardiac shunts</td>
<td>• Cardiac shunts</td>
<td>• Cardiac shunts</td>
</tr>
<tr>
<td>• Intra-arterial injection</td>
<td>• Intra-arterial injection</td>
<td>• Intra-arterial injection</td>
<td>• Intra-arterial injection</td>
</tr>
<tr>
<td>• Serious cardiopulmonary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>conditions*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Warnings</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Compromised pulmonary vascular bed</td>
<td>Black box warning¹</td>
<td>• Black box warning²</td>
<td>• Black box warning³</td>
</tr>
<tr>
<td>• Black box warning²</td>
<td>• Serious cardiopulmonary conditions*</td>
<td>• Serious cardiopulmonary conditions*</td>
<td></td>
</tr>
<tr>
<td><strong>Additional guidance</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Safety in mechanically</td>
<td>• Safety of DEFINITY with high mechanical index or end-systolic triggering not established</td>
<td>• Safety of DEFINITY with high mechanical index or end-systolic triggering not established</td>
<td>• Safety of DEFINITY with high mechanical index or end-systolic triggering not established</td>
</tr>
<tr>
<td>ventilated patients not</td>
<td>• Safety of DEFINITY with high mechanical index or end-systolic triggering not established</td>
<td>• Safety of DEFINITY with high mechanical index or end-systolic triggering not established</td>
<td>• Safety of DEFINITY with high mechanical index or end-systolic triggering not established</td>
</tr>
<tr>
<td>established</td>
<td>• Safety/efficacy in stress testing not established</td>
<td>• Safety/efficacy in stress testing not established</td>
<td>• Safety/efficacy in stress testing not established</td>
</tr>
<tr>
<td>• Safety of DEFINITY with high mechanical index or end-systolic triggering not established</td>
<td>• Potential for anaphylactoid reactions</td>
<td>• Potential for anaphylactoid reactions</td>
<td>• Potential for anaphylactoid reactions</td>
</tr>
<tr>
<td>• Potential for anaphylactoid reactions</td>
<td>• 30-minute monitoring period in all patients</td>
<td>• 30-minute monitoring period only in patients with serious cardiopulmonary conditions* or pulmonary hypertension</td>
<td>• Serious adverse reactions are ‘uncommon’ and ‘occur within 30 minutes of administration’</td>
</tr>
<tr>
<td>• 30-minute monitoring period in all patients</td>
<td></td>
<td></td>
<td>• Deletion of 30 minute monitoring period</td>
</tr>
<tr>
<td>• Deletion of statement regarding lack of safety/efficacy data in stress testing</td>
<td></td>
<td></td>
<td>• Deletion of statement regarding lack of safety/efficacy data in stress testing</td>
</tr>
<tr>
<td>• Potential for anaphylactoid reactions</td>
<td></td>
<td></td>
<td>• Inclusion of open-label registry data in 1,053 patients</td>
</tr>
<tr>
<td>• Inclusion of data from pulmonary hemodynamic study in 32 patients</td>
<td></td>
<td></td>
<td>• Inclusion of data from pulmonary hemodynamic study in 32 patients</td>
</tr>
</tbody>
</table>

*Patil H., Main ML. US Cardiology 2012;9:35-9*
### Results of the 6 Safety Studies Designed in Conjunction with FDA

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Pulmonary Hemodynamic Study</th>
<th>Critically Ill Propensity Matched Database</th>
<th>Routine Clinical Care Registry</th>
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</thead>
<tbody>
<tr>
<td>Lantheus Medical Imaging</td>
<td>n=32</td>
<td>n=15,798 propensity matched patients</td>
<td>n=1053</td>
</tr>
<tr>
<td></td>
<td>No change in PA pressure with DEFINITY®</td>
<td>HR=0.683 (0.591-0.789)</td>
<td>No deaths or serious adverse events at 24 hours</td>
</tr>
<tr>
<td></td>
<td>No deaths or SAE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GE Healthcare</td>
<td>n=30</td>
<td>N=2884 propensity matched patients</td>
<td>n=1039</td>
</tr>
<tr>
<td></td>
<td>No change in PA pressure with Optison</td>
<td>(HR=1.4 (0.965-2.030)</td>
<td>No deaths or serious adverse events</td>
</tr>
<tr>
<td></td>
<td>No deaths or SAEs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/ucm254389.htm
Contrast Echocardiography as a Percentage of Total Echocardiography

Arlington Medical Resources

FDA Black Box Warning

2005 2006 2007 2008 2009 2010 2011 2012

Contrast Echocardiography Percentage:
- 2005: 2.5%
- 2006: 2.5%
- 2007: 2.5%
- 2008: 0.5%
- 2009: 1.0%
- 2010: 2.0%
- 2011: 2.0%
- 2012: 2.0%

Arlington Medical Resources
Black Box WARNING Increased Adverse Event Reporting
Acute Hypersensitivity Reactions

IgE mediated type I
- Reaction after repeated exposure
- Reaction is stronger upon repeated exposure
- Reaction does not cease without treatment
- Low reaction rate

CARPA
- No prior exposure necessary
- Reaction is milder or absent upon repeated exposures
- Spontaneous resolution
- Higher reaction rate

Szebeni J. Toxicology 2005:216:106-121
Complement Activation Related Pseudo Allergy (CARPA)

Commonly prescribed drugs which may elicit CARPA

– Radiocontrast media
– Ultrasound contrast agents
– NSAIDs
– Analgetics
– Morphine
– Insect venom
– Liposomes
– Micellar solvents (Cremophor EL (CrEL in Taxol))

Szebeni J. Toxicology 2005:216:106-121
Complement Activation Related Pseudo Allergy (CARPA)

Common Signs and Symptoms

- Angioedema
- Bronchospasm
- Cyanosis
- Hypotension
- Low back pain
- Pruritis
- Urticaria
- Tingling Sensation
- Hypoxemia
- Sneezing

Szebeni J. Toxicology 2005:216:106-121
Lab Efficiency is Key to Better Outcomes

- Commitment to following guidelines
- Strong lead Sonographer/Lab Director/Medical Director establishing and enforcing policy
- Established written clinical policy for use of contrast and non-contrast echo
- Established “operational” policy for contrast use
- Awareness of implications of sub-optimal studies
- Nursing education and commitment
- Standing orders for contrast
GUIDELINES AND STANDARDS

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

Thomas R. Porter, MD, FASE (Chair), Sahar Abdelmonem, MD, J. Todd Belcik, BS, RCS, RDCS, FASE, Marti L. McCulloch, MBA, RDCS, FASE, Sharon L. Mulvagh, MD, FASE, Joan J. Olson, BS, RDCS, RVT, FASE, Charlene Porcelli, BS, RDCS, RDMS, FASE, Jeane M. Tsutsui, MD, and Kevin Wei, MD, FASE, Omaha, Nebraska; Rochester, Minnesota; Portland, Oregon; Houston, Texas; Charleston, South Carolina; São Paulo, Brazil

(J Am Soc Echocardiogr 2014;27:797-810.)
Saline and Transpulmonary Contrast. The appropriateness and use of transpulmonary contrast for endocardial border definition as well as Doppler enhancement is well defined in the 2014 ASE contrast guidelines. Additional uses of transpulmonary contrast can include border and structure definition of thrombi (Figure 4) and masses as well as showing if a structure is vascularized, much like cardiac MRI.

Although color Doppler can sometimes detect intracardiac communication, the use of agitated saline contrast yields higher results or incidence of findings (Figure 5).
Clinical applications of ultrasound contrast

left ventricular opacification

myocardial perfusion
Left ventricular contrast opacification with thrombus
Top 10 Reasons That Prevent the Widespread Use of Contrast in the Echo Laboratory

• How many attendees use contrast on a regular basis?
• I don’t need it. Our echos are good enough without contrast.
• It’s a crutch. We are good enough.
• Our Doctors don’t think we need it.
• Our Doctors don’t know how to read contrast studies.
• It costs too much.
• We don’t have a nurse available to inject the contrast.
• The echo machines will be improving and we won’t need to use contrast
• We are waiting for Perfusion.
• September 8-10, 2016

31th year!

The Blackstone Hotel, Chicago, IL.

This unique and exciting international conference plays a vital role in advancing the fields of CEUS imaging and therapy. The annual Chicago "bubble conference" features the world's foremost CEUS key opinion leaders, with a lively, interactive format that encourages networking opportunities and a robust exchange of insights.
Thank you
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• We don’t have a nurse available to inject the contrast.
• The echo machines will be improving and we won’t need to use contrast.
• We are waiting for Perfusion.
Case 1

Acute MI versus Normal LV
Case 2
Post PCI -- Myocardial Perfusion
Case 3

LV Apical Clot or No Clot?
Case 4
Wall Motion abnormalities?
You make the call!
Case 5
Technically difficult echo with contrast LV function and apical clot?
Case 6
VSD – RV to LV
Diastolic transmission of contrast right to left shunting
Case 7
First Stress Echo Stress Echo
With Contrast
January 2, 1998
Case 8

32 year old woman with chest pain
ECG changes inferiorly
Stress echo or cardiac catheterization?
Case 9

Contrast Echo first used in 1988
Case 10
Apical clot?
High versus and low MI
Case 11
Lake Forest CCU
Case #1 CR

60 year old woman in the SICU. Post CABG, hypotensive and tachycardiac. Management: diuretics and sympathomimetics.
Case 13
Case #2 JL

40 year old man, 600 lbs
Pre-operative evaluation
Case 14
Case #3 CS

72 year old man in the SICU. Post CABG, cardiac enzyme elevation and ECG changes.
• 31th Anniversary Conference:
• September 9-10, 2016

31th year!
Blackstone Hotel, Chicago, IL.

This unique and exciting international conference plays a vital role in advancing the fields of CEUS imaging and therapy. The annual Chicago "bubble conference" features the world's foremost CEUS key opinion leaders, with a lively, interactive format that encourages networking opportunities and a robust exchange of insights.