I Hear Contrast is Not Safe, Is That True?
Suboptimal Images: Consequences

- Misdiagnosis
- Low diagnostic confidence
- Need for additional testing procedures
- Interobserver variability

# FDA Approved Contrast Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Size (μm)</th>
<th>Gas</th>
<th>Shell</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optison</td>
<td>3.0-4.5</td>
<td>Perfluoropropane</td>
<td>Albumin</td>
<td>LVO/EBD</td>
</tr>
<tr>
<td>Definity</td>
<td>1.3-3.3</td>
<td>Perfluoropropane</td>
<td>Phospholipid</td>
<td>LVO/EBD</td>
</tr>
<tr>
<td>Lumason (Sonovue)</td>
<td>1.5-2.5</td>
<td>Sulfur hexafluoride</td>
<td>Phospholipid</td>
<td>LVO/EBD</td>
</tr>
</tbody>
</table>
Contrast Applications

- **Left Ventricular Opacification (LVO)**
  - Contrast agent used as marker for blood pool
  - Better endocardial border visualization, i.e. Wall Motion

- **Myocardial Contrast Enhancement (MCE)**
  - Contrast agent used as marker for blood flow in capillary beds, microcirculation
  - Optimized to see low concentrations of agent in myocardium
Contrast Echo: Weaknesses
Underutilization

• Lack of awareness of indications?
• Technology too complicated
• IV initiation?
• Cost/reimbursement? Acceptance of mediocrity
• Inertia?
• Lingering concerns about safety?
FDA Post Marketing Survey

• Temporally related, but not clearly causally attributable to Definity
  
  – (4 patients deaths and approx 190 “serious cardiopulmonary reactions”)

• October 12, 2007
  
  – FDA Black BOX Warning

• May 12, 2008:
  
  – Revision of Black Box Warning
Precluded the use of Perflutren-containing ultrasound contrast agents in the following:

- Worsening or clinically unstable CHF
- Acute MI or ACS
- Serious ventricular arrhythmias
- Respiratory failure
- Severe emphysema
- Pulmonary embolus
- Conditions that cause pulmonary hypertension
- Right-to-left, bidirectional, or transient right-to-left cardiac shunts
- Hypersensitivity to Perflutren
- Intra-arterial injection

All Patients: 30 minutes observation period with vital signs, ECG, o2 sat monitoring

http://www.fda.gov
Contrast Echocardiography as % of echos in USA
>200,000 cardiac patients world-wide, carefully documented, have received echo contrast without evidence of increased death or serious cardiac event.
This multicenter, retrospective analysis includes the largest number of doses of ultrasound contrast agents ever published with a large number of patients evaluated in a wide variety of settings, including the critically ill.

(J Am Soc Echocardiogr 2008;21:1202-1206)
Safety of Definity and Optison

- Contrast agents: 5% of TTE and in 28% of stress studies
- Severe reactions probably related to contrast agents developed in 8 patients (0.01%)
- 4 were anaphylactoid reactions (CARPA)
- Incidence of adverse reactions is lower than that reported for contrast agents commonly used in other cardiac imaging tests
  - Urticaria 0.5%
  - Sudden hypotension 0.3%
  - Cardiac arrest 0.2%

(J Am Soc Echocardiogr 2008;21:1202-1206)
Retrospective analysis of a large database of hospitalized patients undergoing echocardiography compared the acute effects of Definity-enhanced echocardiograms (n=58,254) with un-enhanced studies (n=4,242,712).

While the one-day mortality rates were similar for un-enhanced and contrast studies (1.08 vs. 1.06%), on multivariate logistic regression analysis, those receiving Definity were 24% less likely to die within one day than those not receiving contrast.

Safety and efficacy of contrast for stress echo was retrospectively analyzed in 42,408 patients from three centers.

The risks of both non-fatal myocardial infarction and death were very low (1 death and 5 nonfatal infarctions within 24 hours) and no different than a matched cohort of 18,749 patients who underwent stress echo without contrast.

# Comparative Mortality in Selected Cardiac Procedures

<table>
<thead>
<tr>
<th>Procedures</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contrast Echo</td>
<td>1:45,000 (SonoVue)</td>
</tr>
<tr>
<td></td>
<td>1: 500,000 (Definity)</td>
</tr>
<tr>
<td>Myocardial Scintigraphy</td>
<td>1:10,000</td>
</tr>
<tr>
<td>Exercise EKG</td>
<td>1:2500 (or AMI)</td>
</tr>
<tr>
<td>Coronary arteriography</td>
<td>1:1000</td>
</tr>
</tbody>
</table>

Contrast Ultrasound Anaphylactoid Reactions

CARPA
Complement Activation Related Pseudo Allergy

- Ig-E mediated Type 1 reaction
- Angioedema, bronchospasm, hypoxemia, hypotension, LBP, and urticaria
- Reaction arises at first TX, milder or absent with repeated exposures
Contrast Ultrasound Anaphylactoid Reactions
Complement Activation Related Pseudo Allergy
CARPA

C Activation-related Related Pseudo-allergy and not via Ig-E mediated Type 1

1. Angioedema, bronchospasm, chest pain, lumbar pain, wheezing
2. Reaction arises at first treatment
3. Reaction is milder or absent upon repeated exposures
4. Spontaneous resolution
5. Reaction rate is high

Szebeni J. Toxicology 2005; 216:106-21
FDA Black Box Warning

- Response from international physician community
- New contrast agent safety data published
- Special meeting of FDA Cardio-renal Panel, (May 12, 2008)
- Revision of Black Box warning (May 12, 2008)
- FDA mandated that safety studies be performed in patients with pulmonary hypertension
FDA Revised Contrast Agents Labeling on May 12, 2008

- Black Box remains, but contraindications to contrast agents restored to original labeling
- Right-to-left, bidirectional, or transient right-to-left cardiac shunts
- Hypersensitivity to Perflutren, to blood, to blood products, or albumin
- Intra arterial injection
- 30 min observational period (ECG, O2 sat after Contrast administration in pts with Pulmonary HTN and unstable cardiopulmonary conditions

http://www.fda.gov
The Effect of Optison on Systemic and Pulmonary Hemodynamics in Normal Subjects and Patients with Pulmonary Hypertension
The Effect of Definity on Systemic and Pulmonary Hemodynamics in Patients with Pulmonary Hypertension

Wei K, Main M, Lang RM, Klein A, Angeli S, Panetta C, Mikati, Lee L, Ahmad M
The Effect of Definity on Systemic and Pulmonary Hemodynamics

- Definity® at the approved dosage does not change pulmonary or systemic hemodynamics in control patients or those with mild to moderate pulmonary hypertension.

- No significant changes were noted clinical or laboratory safety assessments after Definity®.

Wei K, Main M, Lang RM et al., 2011
Black Box
Do not administer Perflutren to patients with

1) Known or suspected right-to-left, bidirectional, or transient right-to-left cardiac shunts

2) Hypersensitivity to perflutren

3) Do not administer intra-arterial injection

4) Monitoring only in patients with pulmonary hypertension or unstable cardiopulmonary conditions
Safety of Ultrasound Contrast Agents

• Life threatening reactions are rare (<1:10,000)
  – Less than with contrast agents used in other imaging modalities
• Labs must have policies/procedures for early recognition/Rx of serious anaphylactic reactions
• Pulmonary hypertension does not preclude UCA use
• Patients with PFO are not at increased risk with UCA use
  – JACC Imaging 2014;7:206, J Am Soc Echocardiogr 2013; 112; 1039
Thanks for your attention
# Side Effects

<table>
<thead>
<tr>
<th>Most frequent side effect in clinical trials</th>
<th>Optison (GE)</th>
<th>Definity (Lantheus Medical Imaging)</th>
<th>Lumison (Bracco)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache (5.4%)</td>
<td></td>
<td>Headache (2%)</td>
<td>Headache (2.1%)</td>
</tr>
<tr>
<td>Nausea (4.3%)</td>
<td></td>
<td>Flushing (1.0%)</td>
<td>Nausea (1.3%)</td>
</tr>
<tr>
<td>Flushing (3.6%)</td>
<td></td>
<td>Back pain (0.9%)</td>
<td>Taste perversio</td>
</tr>
<tr>
<td>Dizziness 2.5%</td>
<td></td>
<td>Urticaria, wheezing/ana phylaxis</td>
<td>(0.9%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hyperglycemia</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>(0.6%)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Paresthesia (0.6%)</td>
</tr>
</tbody>
</table>
Summary Safety

• Ultrasound contrast safety is a complex issue; need to consider low risk of contrast agent side effect in sick patients, risk of misdiagnosis/missed diagnosis, and risks of alternative procedures

• No significant safety signal in >200,000 patient doses of contrast agents, low incidence of side effects (less current X-ray or MR contrast agents)

• Approximately 1/10,000 risk of an anaphylactoid reaction

• There is no increase in crude mortality in hospitalized patients undergoing MCE