The Basics of Using Contrast
Optimizing Contrast: How to Give the Contrast Agent

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Microbubble Contrast Agents

- Microbubbles are sized to pass through the smallest capillaries (5 microns)
- Designed to increase signal strength of echo
  - Different acoustic impedance
  - Harmonic signal
3D Echo with Poor Endocardial Definition
3DE with Contrast for LV Volumes

- 4ChDIA Length: 8.91 cm
- 2ChDIA Length: 8.71 cm
- 4ChSYS Length: 7.52 cm
- 2ChSYS Length: 7.81 cm

- Area(s):
  - 4ChDIA = 37.58 cm²
  - 2ChDIA = 33.89 cm²
  - 4ChSYS = 20.22 cm²
  - 2ChSYS = 16.51 cm²

- Volume(s):
  - EDV = 121.48 ml
  - ESV = 40.63 ml

- Calculation(s):
  - EF = 68.55 %
Technique of Bolus Administration

• Use tiny doses (0.1-0.4 ml)
• Never flush vigorously
• Use a very slow saline flush by syringe, or chase the bolus with a saline drip, adjusting the rate to get good imaging
Attenuation by Aggressive Flush
Technique for Definity Infusion

- One vial of Definity in 50 cc saline bag
- Use dial-a-flow for rate adjustment
- Start around 1 drop/sec, adjust up or down to visualize endocardial borders without obliterating the mitral annulus
- Most infusion pumps destroy the bubbles
- Small needles, IVs can destroy bubbles
  - 18G needles, 22G catheter or bigger
Infusion Techniques With DEFINITY®

• Macrodrip IV set or equivalent
  – 1 drop/sec (4 mL/min) initially; use visual inspection
  – Maximum: 10 mL/min
• The rate can be titrated to optimize enhancement
• If unused for >5 min, even distribution of microspheres needs to be ensured by squeezing IV bag gently
Technique for Optison Infusion

• Fill the IV line with Optison
• Chase it in slowly with saline via infusion pump or Dial-a-Flow
• Adjust rate to visualize endocardial borders without obliterating the mitral annulus
• Gently shake the IV line and tap on it to prevent Optison from sticking to the sides and to keep it from separating
Bolus vs. Infusion: Summary

**Bolus**
- Minimal imaging time required
- Higher initial concentrations
- Probable attenuation artifacts

**Infusion**
- Prolongs duration of enhancement
- Consistent level of enhancement
- Less attenuation artifacts
Instrument Settings

- Harmonic imaging
- Lower the mechanical index (MI) to avoid microbubble destruction
- May need to adjust the focus
  - Set at apex to see apical thrombus, wall motion
  - Set at mitral annulus to see leaflet insertion for tracing LV volumes/LVEF
- Use “presets” per manufacturers
Contrast Imaging Modalities

- Harmonic imaging
- Power Doppler
- Pulse Inversion Imaging
- Power Modulation Imaging
- Coherence Imaging
- Ultraharmonic or subharmonic imaging
Tissue vs. Contrast Signal

- Fundamental Tissue
- Harmonic Tissue
- Contrast agent

Graph showing transmit and receive frequencies with MHz on the x-axis.
Set Focus at Mitral Annulus
Lower the MI Setting
Case Examples
Apical 4 Chamber - Normal
After Contrast – Not Normal
Apical 4-Chamber – Poor EBD
Contrast – Lateral Akinesis
S/P Acute Anterior MI

- 63 yr old woman presents with CVA
- ECG shows ST elevation V3-V6 with T wave inversions
- Clinical picture suggests anterior MI occurred at home in past 2-5 days
- TTE ordered to assess LV function, thrombus
LV Hypertrophy vs. Mass
LV Hypertrophy vs. Mass
Large Mass Invading Myocardium
What in the World is This?
Agitated Saline Contrast
Optison Infusion
What Is It?

• Patient spent time in prison for armed robbery
• During the robbery, he was shot in chest
• Bullet went through RV, stopped in LV
• Surgeons removed bullet from LV apex, and performed patch to exclude distal RV, closed hole in RV free wall
• Combination of saline contrast and transpulmonary contrast very helpful
Contrast Safety

Michael L. Main MD FASE
Saint Luke’s Mid America Heart Institute
Kansas City, Missouri
Initial FDA Action in October 2007

• 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
## 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>
</tr>
</thead>
<tbody>
<tr>
<td>Lantheus Medical Imaging</td>
<td>n=32 No change in PA pressure with Definity No deaths or SAE</td>
<td>n=15,798 propensity matched patients HR=0.683 (0.591-0.789)</td>
<td>n=1053 No deaths or serious adverse events at 24 hours</td>
</tr>
<tr>
<td>GE Healthcare</td>
<td>n=30 No change in PA pressure with Optison No deaths or SAEs</td>
<td>N=2884 propensity matched patients (HR=1.4 (0.965-2.030)</td>
<td>n=1039 No deaths or serious adverse events</td>
</tr>
</tbody>
</table>

http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/ucm254389.htm
### Meta-Analysis of Adverse Cardiovascular Events Associated with Echocardiographic Contrast Agents

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Contrast Events Total</th>
<th>No Contrast Events Total</th>
<th>Weight %</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdelmoneim</td>
<td>37 10792</td>
<td>57 15982</td>
<td>20.6%</td>
<td>0.96 [0.64, 1.45]</td>
<td></td>
</tr>
<tr>
<td>Anantharam</td>
<td>0 1150</td>
<td>0 2554</td>
<td>Not estimable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dolan</td>
<td>37 42408</td>
<td>62 23812</td>
<td>20.7%</td>
<td>0.33 [0.22, 0.50]</td>
<td></td>
</tr>
<tr>
<td>Gabriel</td>
<td>10 4786</td>
<td>16 5012</td>
<td>16.0%</td>
<td>0.65 [0.30, 1.44]</td>
<td></td>
</tr>
<tr>
<td>Kusnetzky</td>
<td>26 12475</td>
<td>46 6196</td>
<td>19.8%</td>
<td>0.28 [0.17, 0.45]</td>
<td></td>
</tr>
<tr>
<td>Main</td>
<td>616 58254</td>
<td>457894 4242712</td>
<td>23.0%</td>
<td>0.98 [0.90, 1.06]</td>
<td></td>
</tr>
<tr>
<td>Shaikh</td>
<td>0 2914</td>
<td>0 2155</td>
<td>Not estimable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wei</td>
<td>0 78383</td>
<td>0 780243</td>
<td>Not estimable</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Total (95% CI):**
- Contrast: 211162 (5078666 100.0%)
- No Contrast: 5078666 100.0%
- Odds Ratio: 0.57 [0.32, 1.01]

**Total events:**
- Contrast: 726
- No Contrast: 45970

**Heterogeneity:**
- Tau^2 = 0.36; Chi^2 = 50.27; df = 4 (P < 0.00001); P = 92%

**Test for overall effect:**
- Z = 1.93 (P = 0.05)

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**Figure 2.** Pooled OR for all-cause mortality across studies between patients undergoing and not undergoing contrast imaging.
Meta-Analysis of Adverse Cardiovascular Events Associated with Echocardiographic Contrast Agents

### 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><strong>Total</strong></td>
<td>110,500 (excluding NA studies)</td>
<td><strong>11 (0.009%)</strong></td>
<td><strong>5 (0.004%)</strong></td>
</tr>
</tbody>
</table>

NA = not applicable.
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

Szebeni J. Toxicology 2005:216:106-121
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
Allergy Kit Inventory List

Medications
– Albuterol inhaler
– Atropine
– Benadryl
– Epinephrine (1000u/ml, 10,000u/ml, Epi Pen)
– Glucagon
– Lasix
– Solu-medrol

Supplies
– Syringes (1cc, 3cc, 5cc, 10cc)
– Needles (18g blunt, filter)
– Adhesive Tape
– Angiocaths (16g, 18g, 20g, 22g)
– Extension Set
– Injection Cap (needle port, leur lock)
– Alcohol pads
– 2x2 guaze pads

Oxygen Cylinder (regulator, wrench)
– Nasal Cannula, NRB Mask
Allergy Kit
Consent Form

INTRAVENOUS CONTRAST ADMINISTRATION WITH DEFINITY ® OR OPTISON™
INFORMED CONSENT

Your doctor has scheduled you for an echocardiogram. This test may require an injection of a contrast agent. The contrast agent is necessary to address specific questions and help the cardiologist interpret your study.

Definity® and Optison™ are FDA approved. They are different from x-ray contrast agents and do not contain iodine. Common side effects include transient lower back discomfort or flushing that resolve within minutes. Rarely, a more serious reaction may occur (1 out of 10,000 injections). The healthcare providers working with you today are trained and equipped to assist you promptly should any problem occur. The cardiologists within the Saint Luke’s Health System are aware of the very small risk of complication and feel that the diagnostic information to be obtained outweighs any potential risk. We take every precaution to follow the guidelines for use set forth by the FDA to ensure safety.

I, ____________________________________, have read and understand the above and give consent to have an injection of Definity® or Optison™ as part of my echocardiogram evaluation.

Signature of Patient        Date

Signature of Witness        Date
## Changes to Product Label

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

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Patil H., Main ML. US Cardiology 2012;9:35-9
Synopsis of Suggested Applications for Ultrasound Contrast Agent Use

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
82 year-old man presents with left arm pain and nausea

Apical 4-chamber
Contrast enhanced image reveals a large zone of apical dyskinesis
Apical mural thrombus or not?

- 45 year-old man with known coronary artery disease
- Percutaneous coronary intervention in 2003
Apical mural thrombus or not?

- 45 year-old man with known coronary artery disease
- Percutaneous coronary intervention in 2003

Apical 4-chamber
Contrast Enhanced Examination

Contrast enhanced image reveals a large left ventricular apical mural thrombus
Recent Anterior Myocardial Infarction and Possible Apical Thrombus
Contrast Enhanced Image

Baseline Image

Contrast Enhanced Image
Markedly Improved Echocardiographic Detection of Left Ventricular Thrombus with Ultrasound Contrast Agents

Table 3. Diagnostic Performance of Anatomic Imaging for LV Thrombus*

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noncontrast echocardiography</td>
<td>33% (8/24)</td>
<td>94% (91/97)</td>
<td>82% (99/121)</td>
<td>57% (8/14)</td>
<td>85% (91/107)</td>
</tr>
<tr>
<td>Contrast echocardiography†</td>
<td>61% (14/23)‡</td>
<td>99% (96/97)</td>
<td>92% (110/120)§</td>
<td>93% (14/15)</td>
<td>91% (96/105)</td>
</tr>
<tr>
<td>Cine-CMR</td>
<td>79% (19/24)†</td>
<td>99% (96/97)</td>
<td>95% (115/121)†</td>
<td>95% (19/20)</td>
<td>95% (96/101)</td>
</tr>
</tbody>
</table>

*Values in parentheses represent counts of true positives and negatives.
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
HeartMate II Left Ventricular Assist Device
Left Ventricular Apical Pseudoaneurysm
Increasing Prevalence of Clinically Severe Obesity in Patients Referred for Echocardiography

<table>
<thead>
<tr>
<th>BMI Categories</th>
<th>2002 (n = 10,804)</th>
<th>2006 (n = 17,556)</th>
<th>p Value</th>
<th>Percent Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18.5</td>
<td>306 (2.8%)</td>
<td>463 (2.6%)</td>
<td>0.326</td>
<td>7.1%</td>
</tr>
<tr>
<td>19.0–24.99</td>
<td>3,397 (31.4%)</td>
<td>5,160 (29.4%)</td>
<td>&lt;0.001</td>
<td>-6.4%</td>
</tr>
<tr>
<td>25.0–29.99</td>
<td>3,615 (33.5%)</td>
<td>5,675 (32.3%)</td>
<td>0.048</td>
<td>-3.6%</td>
</tr>
<tr>
<td>30.0–39.99</td>
<td>2,818 (26.1%)</td>
<td>4,942 (28.1%)</td>
<td>&lt;0.001</td>
<td>7.7%</td>
</tr>
<tr>
<td>40.0–49.99</td>
<td>542 (5.0%)</td>
<td>1,011 (5.8%)</td>
<td>0.008</td>
<td>16%</td>
</tr>
<tr>
<td>&gt;50</td>
<td>126 (1.2%)</td>
<td>305 (1.7%)</td>
<td>&lt;0.001</td>
<td>41.7%</td>
</tr>
</tbody>
</table>

18 Year Old Man with Super Obesity (BMI=58.3) and Dyspnea
Is There LV Dysfunction?
Contrast Enhanced Image

LVEF=11%, Global Hypokinesis, LVEDI=123mL
34 Year Old Super Obese Woman (BMI=64.2)
Is LVEF Normal?
Contrast Enhanced Image
Clearly Normal LV Function
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

Impact of Contrast Echocardiography on Evaluation of Ventricular Function and Clinical Management in a Large Prospective Cohort

• Methods: Clinicians advised of baseline study and management decisions recorded; next informed of contrast study results and changes in management plan recorded

Total Impact of Contrast on Patient Management

Recent Joint Commission Statement on Radiation Risks of Diagnostic Imaging

“In order to reduce the exposure of the patient to ionizing radiation, use other imaging techniques, such as ultrasound or MRI, whenever these tests will produce the required diagnostic information at a similar quality level”

### Table 18: Contrast use in TTE/TEE or stress echocardiography

<table>
<thead>
<tr>
<th>Indication</th>
<th>Appropriate use score (1–9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>201. Routine use of contrast</td>
<td>1 (1)</td>
</tr>
<tr>
<td>All LV segments visualized on noncontrast images</td>
<td></td>
</tr>
<tr>
<td>202. Selective use of contrast</td>
<td>A (3)</td>
</tr>
<tr>
<td>≥2 contiguous LV segments are not seen on noncontrast images</td>
<td></td>
</tr>
</tbody>
</table>

A indicates appropriate; I, inappropriate; U, uncertain.