ULTRASOUND CONTRAST AGENTS
BASIC PRINCIPLES AND APPLICATIONS
Jason E. Streeter & Paul A. Clayton

DISCUSSION POINTS
• Part I
  • Microbubble Basics
  • Fundamentals in Contrast Imaging
  • Basic Imaging Applications
• Part II
  • Advanced Imaging Applications
  • Bioeffects and Therapeutic Applications
  • Safety

PART I
MICROBUBBLE INTRODUCTION

• What are Microbubble Contrast Agents?
  • Gas: Air, Perfluorocarbon, Sulfur Hexafluoride, etc.
  • Shell: Polymer, Lipid, Albumin, etc.
  • Size: Typically < 8 µm (Size of RBC)
  • Confined to the Vascular Space

MICROBUBBLE INTRODUCTION

• Examples

WHY MICROBUBBLES?

• Microbubbles and Ultrasound
  • Highly Echogenic
MICROBUBBLE PROPERTIES

• Microbubbles and Ultrasound
  • **Highly Echogenic**
    - Dependent on acoustic impedance differences
    - Acoustic impedance = Density * SoS

Water: 1.50 Mrayls
Brain: 1.56 Mrayls
Bone: 1.4 Mrayls
Muscle: 1.6 Mrayls
Fat: 1.33 Mrayls

Orders of Magnitude Difference

Tissue: 1.54 Mrayls
Air: 0.0004 Mrayls

MICROBUBBLE PROPERTIES

• Microbubbles in an Ultrasound Field
  • Highly Echogenic
  • **Oscillate**
    - Oscillation governed by...
      1) Frequency
      2) Pressure Amplitude
      3) Pulse Repetition Frequency
      4) Type of Gas Core
      5) Damping Coefficients
      6) Shell Properties

MICROBUBBLE PROPERTIES

- Microbubbles in an Ultrasound Field
  - Highly Echogenic
  - **Oscillate**

Stable Oscillation

Unstable Oscillating Behavior

MICROBUBBLE PROPERTIES

- Microbubbles in an Ultrasound Field
  - Highly Echogenic
  - Oscillate

![Resonance Curve](image)


- Attenuate
  - Shadowing
  - Tissue Artifact

Example 1: Contrast Imaging

Kidney


MICROBUBBLE PROPERTIES

- Describing the Motion of a Microbubble
  - Rayleigh - Plesset

\[ \rho_R \frac{\partial^2 R}{\partial t^2} + \frac{3}{2} \rho_R \frac{\partial R}{\partial t} = \rho_0 - \rho_m R = \rho_0 - \rho_R. \]

MICROBUBBLE PROPERTIES

- Describing the Motion of a Microbubble
  - Rayleigh – Plesset

\[ \rho R R' + \frac{3}{2} \rho R'^2 = p_i - p_o \rho R'' + p_i - p_o \]

\( \rho \) = Density of Medium

\( R \) = Microbubble Radius

\( R' \) = 1st Time Derivative of Radius

\( R'' \) = 2nd Time Derivative of Radius

\( p_i \) = Liquid Pressure at Wall

\( p_o \) = Liquid Pressure Away From Wall


MICROBUBBLE PROPERTIES

- Describing the Motion of a Microbubble
  - Rayleigh – Plesset
  - Including Shell Properties
    - Viscosity of the Shell
    - Elasticity of the Shell

\[ \rho R R' + \frac{3}{2} \rho R'^2 = p_i - p_o \rho R'' - \frac{2 \eta}{R} - \frac{4 \rho R'}{R} - p_i \sin(wt) \]

\( S \) = Surface Tension

\( \eta \) = Liquid Shear Viscosity


MICROBUBBLE PROPERTIES

- Describing the Motion of a Microbubble
  - Rayleigh – Plesset
  - Including Shell Properties
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\[ \rho R R' + \frac{3}{2} \rho R'^2 = p_i - p_o \rho R'' - \frac{2 \eta}{R} - \frac{4 \rho R'}{R} - p_i \sin(wt) \]

MICROBUBBLE PROPERTIES

• Describing the Motion of a Microbubble
  • Rayleigh – Plesset
  • Including Shell Properties
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    • Elasticity of the Shell
  • Complex Equation → Difficult to model and simulate


MICROBUBBLE PROPERTIES

• Describing the Motion of a Microbubble
  • Rayleigh – Plesset
  • Including Shell Properties
    • Viscosity of the Shell
    • Elasticity of the Shell
  • Complex Equation → Difficult to model and simulate
  • Concentration and Size Distributions Exacerbate Complexity!


MICROBUBBLE PROPERTIES

• Microbubble Destruction Increases for...
  • High Pressure Amplitudes

Chomas J, et al... Threshold of fragmentation for ultrasonic contrast Agents. Journal of Biomedical Optics 6(2), pg. 141-150; 2001
MICROBUBBLE PROPERTIES

- Microbubble Destruction Increases for...
  - **Low Frequencies**


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MICROBUBBLE PROPERTIES

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  - Low Frequencies
  - **Long Ultrasound Pulse Lengths**


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MICROBUBBLE PROPERTIES

- Microbubble Destruction Increases for...
  - High Pressure Amplitudes
  - Low Frequencies
  - Long Ultrasound Pulse Lengths
  - **Most Important: High Pressure Amplitude, Low Frequency**

BASIC CONTRAST IMAGING TECHNIQUES

IMAGING MICROBUBBLES

- Microbubble Response Related to Insonation Frequency

Insonation Waveform

\[ \mathcal{F} \]

Fourier Domain

\[ f_0 \]


- Microbubble Response Related to Insonation Frequency

Insonation Parameters: 20 Cycle, 2.25 MHz

IMAGING MICROBUBBLES

- Microbubble Response Related to Insonation Frequency
- Microbubble Response is Non-Linear

Transmission Pulse: Pressure
Bubble Response: Expansion is Not the Same as Contraction!

IMAGING MICROBUBBLES

- Microbubble Response Related to Insonation Frequency
- Microbubble Response is Non-Linear
- **Microbubbles Generate Harmonic and Sub Harmonic Energy**

Sub-Harmonic Example:

![Image showing microbubble response to insonation frequency](image)


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IMAGING MICROBUBBLES

- Microbubble Response Related to Insonation Frequency
- Microbubble Response is Non-Linear
- Microbubbles Generate Harmonic and Sub Harmonic Energy
- **Imaging Techniques Take Advantage of Microbubble Properties**


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IMAGING MICROBUBBLES

- Microbubble Response Related to Insonation Frequency
- Microbubble Response is Non-Linear
- Microbubbles Generate Harmonic and Sub Harmonic Energy
- Imaging Techniques Take Advantage of Microbubble Properties
- **Goal: Separate Microbubble Signal From Tissue**

HARMONIC IMAGING

- Transducer has Finite Bandwidth

Transducer Bandwidth

BW


HARMONIC IMAGING

- Insonify Microbubbles at Frequency \( f \)

Transmit Frequency


HARMONIC IMAGING

- Receive Echo at Frequency \( 2f \)

Receive Frequency BW

HARMONIC IMAGING

- High Pass Filter Received Signal

Filter Pass Band


HARMONIC IMAGING

- Strong Tissue Signal Can Overpower Weak Harmonic!

Filter Pass Band


SUBHARMONIC IMAGING

- Microbubbles have Subharmonic Energies

SUBHARMONIC IMAGING

- Microbubbles have Subharmonic Energies
- **Occur at ~1/2 of the Transmitted Frequency**


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SUBHARMONIC IMAGING

- Microbubbles have Subharmonic Energies
- **Response at ~1/2 of the Transmitted Frequency**


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SUBHARMONIC IMAGING

- Microbubbles have Subharmonic Energies
- Response at ~1/2 of the Transmitted Frequency
- **Tissue Does Not Generate Sub Harmonic Energy**

SUB HARMONIC IMAGING

- Microbubbles have Subharmonic Energies
- Response at ~1/2 of the Transmitted Frequency
- Tissue Does Not Generate Sub Harmonic Energy
- Sub Harmonic Imaging
  - Easy Separation from Tissue
  - Lower Frequencies Mean Less Attenuation

SUB HARMONIC IMAGING

- Microbubbles have Subharmonic Energies
- Response at ~1/2 of the Transmitted Frequency
- Tissue Does Not Generate Sub Harmonic Energy
- Sub Harmonic Imaging
  - Easy Separation from Tissue
  - Lower Frequencies Mean Less Attenuation
  - Low Frequency Trade-off with Resolution


PULSE INVERSION TECHNIQUES

- Transmitted US Pulse
- Tissue (Linear)
- US Beam
- Microbubble (Non-linear)
- Response from Linear Target
- Response from Non-linear Target
PULSE INVERSION TECHNIQUES

Transmitted US Pulse

Response from Linear Target

Response from Non-Linear Target

US Beam

Microbubble (Non-linear)

Transducer

Microbubble (Non-linear)

Tissue (Linear)

Time
PULSE INVERSION TECHNIQUES

Transmitted US Beam

Transmitted US Pulse

Linear (Tissue)

Bubble (Non-linear)

Time

A

B

A+B

AMPLITUDE MODULATION TECHNIQUES

COMBINING TECHNIQUES

Example:
Siemens Sequoia – 15L8 Linear Array Transducer
Cadence Pulse Sequencing Mode (Contrast Imaging)
Amplitude Modulation and Pulse Inversion

Traditional B-Mode
Contrast Mode
Overlay

Tumor
Non-Linear Contrast
Tissue Artifact

Streeter - Unpublished Data.

IMAGING TECHNIQUES SUMMARY

• Single Pulse Strategies
  - Harmonic Imaging
    - Advantage: Interference with Tissue Signal
  - Sub-Harmonic Imaging
    - Advantage: Low Frequency = Poor Resolution
• Post-Processing Strategies
  - Pulse Inversion
    - Advantage: Lower Frame Rate, Sensitive to Tissue Motion
  - Amplitude Modulation
    - Advantage: Lower Frame Rate, Sensitive to Tissue Motion
• Most Systems Today Incorporate Some Combination!

BASIC IMAGING APPLICATIONS
CONTRAST-ENHANCED ULTRASOUND

• Blood is a Weak Scatterer

• Microbubbles Help Delineate Tissue From Blood

• Provides Clearer Picture For Clinicians

CONTRAST-ENHANCED ULTRASOUND

- Blood is a Weak Scatterer
- Microbubbles Help Delineate Tissue From Blood
  - Provides Clearer Picture For Clinicians
- Ability to Quantify Tissue Perfusion
- Transit Time Measurements


CONTRAST-ENHANCED ULTRASOUND

- Blood is a Weak Scatterer
- Microbubbles Help Delineate Tissue From Blood
  - Provides Clearer Picture For Clinicians
- Ability to Quantify Tissue Perfusion
  - Transit Time Measurements
- Evaluation of Blood Volume

CONTRAST-ENHANCED ULTRASOUND
• Blood is a Weak Scatterer
• Microbubbles Help Delineate Tissue From Blood
  • Provides Clearer Picture For Clinicians
• Ability to Quantify Tissue Perfusion
  • Transit Time Measurements
  • Evaluation of Blood Volume
  • Replenishment Kinetics


CONTRAST ECHOCARDIOGRAPHY
• Assessment of Left Ventricular Cavity


CONTRAST ECHOCARDIOGRAPHY
• Assessment of Left Ventricular Cavity
  • Requires Endocardial Border Visualization

CONTRAST ECHOCARDIOGRAPHY

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  • Requires Endocardial Border Visualization
  • Adequate Visualization Not Possible in 15% of Patients


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  • Left Ventricular Opacification


CONTRAST ECHOCARDIOGRAPHY

• Assessment of Left Ventricular Cavity
  • Requires Endocardial Border Visualization
  • Adequate Visualization Not Possible in 15% of Patients
  • Left Ventricular Opacification
    • Microbubbles Improve Visualization

CONTRAST ECHOCARDIOGRAPHY

• Assessment of Left Ventricular Cavity
  • Requires Endocardial Border Visualization
  • Adequate Visualization Not Possible in 15% of Patients
• Left Ventricular Opacification
  • Microbubbles Improve Visualization
  • Produces Homogenous Opacification


CONTRAST ECHOCARDIOGRAPHY

• Assessment of Left Ventricular Cavity
  • Requires Endocardial Border Visualization
  • Adequate Visualization Not Possible in 15% of Patients
• Left Ventricular Opacification
  • Microbubbles Improve Visualization
  • Produces Homogenous Opacification
  • Improves Reader Accuracy and Confidence


CONTRAST ECHOCARDIOGRAPHY

4 Chamber View 2 Chamber View

Poor Endocardial Definition

CONTRAST ECHOCARDIOGRAPHY

4 Chamber View  2 Chamber View

Poor Endocardial Definition

Improved Definition Due to Contrast


TIME INTENSITY CURVE

• Contrast-Enhanced Monitoring Over Time


TIME INTENSITY CURVE

• Contrast-Enhanced Monitoring Over Time
  • Select a Region of Interest

TIME INTENSITY CURVE

• Contrast-Enhanced Monitoring Over Time
• Select a Region of Interest
• Evaluate the Intensity of the Microbubbles

TIME INTENSITY CURVE

- Contrast-Enhanced Monitoring Over Time
- Select a Region of Interest
- Evaluate the Intensity of the Microbubbles

How It Works:

TIME INTENSITY CURVE
- Contrast-Enhanced Monitoring Over Time
- Select a Region of Interest
- Evaluate the Intensity of the Microbubbles
- Example:
  - Evaluation of Liver Lesions

DESTRUCTION-REPERFUSION

• Perfusion Quantification Helps Understand Diseased Tissue

Quaia E. Assessment of tissue perfusion by contrast-enhanced ultrasound. Eur Radiol: 21 (3); 2011.

DESTRUCTION-REPERFUSION

• Perfusion Quantification Helps Understand Diseased Tissue
  • Microbubbles are Continuously Infused

DESTRUCTION-REPERFUSION

• Perfusion Quantification Helps Understand Diseased Tissue
  • Microbubbles are Continuously Infused
    • Steady State Clearance Equals the Inflow

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DESTRUCTION-REPERFUSION

• Perfusion Quantification Helps Understand Diseased Tissue
• Microbubbles are Continuously Infused
  • Steady State Clearance Equals the Inflow
• Microbubble Destruction in a Single Plane

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DESTRUCTION-REPERFUSION

• Perfusion Quantification Helps Understand Diseased Tissue
• Microbubbles are Continuously Infused
  • Steady State Clearance Equals the Inflow
• Microbubble Destruction in a Single Plane
• Monitoring Microbubble Refill Rate

Quaia E. Assessment of tissue perfusion by contrast-enhanced ultrasound. Eur Radiology: 21 (3); 2011.

DESTRUCTION-REPERFUSION

• Perfusion Quantification Helps Understand Diseased Tissue
• How Does It Work?

[Diagram showing Transducer, Interrogation Plane, Microbubble, Intensity vs. Time graph]
DESTRUCTION-REPERFUSION

• Perfusion Quantification Helps Understand Diseased Tissue
• How Does It Work?

1. Record Intensity
2. Transducer
3. Time
4. Intensity
5. Destroy Microbubbles
6. Monitor Refill

Graph showing the intensity over time.
DESTRUCTION-REPERFUSION

- Perfusion Quantification Helps Understand Diseased Tissue
- **How Does It Work?**

- Record Intensity
- Destroy Microbubbles
- Monitor Refill

---

DESTRUCTION-REPERFUSION

- Perfusion Quantification Helps Understand Diseased Tissue
- What Information Do We Get?
  - Time To Peak Intensity
  - Blood Flow Velocity (Slope)
DESTRUCTION-REPERFUSION

- Perfusion Quantification Helps Understand Diseased Tissue
- What Information Do We Get?
  - Time To Peak Intensity
  - Blood Flow Velocity (Slope)
  - Fractional Blood Volume (Max Amplitude)
  - Blood Volume (Area Under the Curve)
  - Mean Transit Time
DESTRUCTION-REPERFUSION

- Perfusion Quantification Helps Understand Diseased Tissue
- Example:
  - Destruction-Reperfusion at Pixel Level


DESTRUCTION-REPERFUSION

- Perfusion Quantification Helps Understand Diseased Tissue
- Example:
  - Destruction-Reperfusion at Pixel Level
  - Monitoring Time to 20% (Max Intensity)


DESTRUCTION-REPERFUSION

- Perfusion Quantification Helps Understand Diseased Tissue
- Example:
  - Destruction-Reperfusion at Pixel Level
  - Monitoring Time to 20% (Max Intensity)
  - Tumor Perfusion Monitoring During Therapy

DESTRUCTION-REPERFUSION

- Perfusion Quantification Helps Understand Diseased Tissue
- Example:
  - Destruction-Reperfusion at Pixel Level
  - Monitoring Time to 20% (Max Intensity)

More Purple and Red

Day 0  Day 2  Day 14

Treated  Not Treated

20 Sec  0 Sec

PART II
ADVANCED IMAGING APPLICATIONS

MOLECULAR IMAGING
- Functional technique to evaluate changes on a molecular level
- Knowledge of molecular signature of pathology
  - Integrins, selectins etc… expressed on endothelial cells
  - VEGF, αβ3, etc…


MOLECULAR IMAGING
- Targeted microbubble contrast agents
  - Shell material fitted with adhesion ligand
  - Example: αβ3 Ligand → Cyclic RGD Peptide

Dayton et al., Mol Imaging. 2004 Apr;3(2):125-34.
MOLECULAR IMAGING
- Targeted contrast agents injected intravascularly
- Collect at site of desired molecular marker expression
- Determine the presence or absence of a molecular change
- Assess disease or pathology prior to anatomical changes appear

Dayton et al., Mol Imaging. 2004 Apr;3(2):125-34.

MI & RESPONSE TO THERAPY
- Traditional methods for quantifying tumor progression – volume
  - RECIST (Response Evaluation Criteria In Solid Tumors)
  - Size measurements provide delayed feedback
  - Molecular imaging assesses molecular changes often before tumor size is affected

MI & RESPONSE TO THERAPY
- Example:
  - Cancer Type: Human Pancreatic Adenocarcinoma
  - Animal Model: Mouse
  - Therapy: Experimental Aurora-A Kinase Inhibitor
  - Imaging target: αβ3

Molecular imaging of therapeutic response

Status of MI

- Mainly pre-clinical use
- Clinical Trials in Europe
  - Bracco, VEGFR2 targeted imaging in human prostate

Acoustic Angiography

- Goal:
  - Image microvasculature structure
  - Microvascular abnormalities/angiogenesis associated with malignancy

ACOUSTIC ANGIOGRAPHY

Requires:
- High resolution
- Tissue background suppression
- “Very-high-harmonic imaging”

Standard Clinical-Frequency Contrast Imaging

**Frequency [MHz]**

<table>
<thead>
<tr>
<th>0</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
<th>25</th>
<th>30</th>
<th>35</th>
<th>40</th>
<th>45</th>
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**Rx Bandwidth**

**Microbubble Response**

**Tx Bandwidth**


High Frequency Contrast Imaging

**Frequency [MHz]**

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**Rx Bandwidth**

**Microbubble Response**

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High Pass Filter

**Frequency [MHz]**

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**Rx Bandwidth**

**Microbubble Response**

**Tx Bandwidth**

**High Pass Filter**

ACOUSTIC ANGIOGRAPHY

Advantages
- High Frequency - High Resolution
- Attenuation in One Direction
- Eliminates Low Frequency Tissue Signal
- Less Sensitive to Breathing Artifacts

Disadvantages
- Transducers not yet commercial
- High attenuation (shallow depth imaging)
- Not a low-MI imaging technique
HOW ULTRASOUND ANGIOGRAPHY CAN BE USED IN ONCOLOGY RESEARCH:

- Blood vessel structure, density, and pattern can be assessed non-invasively
- Microvascular tortuosity abnormalities are an indicator of tumor development
- Prior studies have shown that vessel morphological characteristics are related to tumor malignancy and response to treatment (Bullitt)


Acoustic Angiography

- Traditional Ultrasound Transducer
  - Transmit and Receive (x1 Frequency Bandwidth)
- Dual Frequency Imaging
  - Transmit Using Low Frequency Bandwidth
  - Receive Using High Frequency Bandwidth


SUMMARY: DIAGNOSTIC IMAGING WITH MICROBUBBLES

- perfusion imaging **
- quantitative dynamic perfusion imaging
- molecular imaging
- acoustic angiography

** only perfusion imaging is currently used clinically in the US
ULTRASONIC ACTIVATABLE CONTRAST AGENTS

- Liquid Perfluorocarbon Core
- Lipid or Polymer Shell
- Tipped to Gaseous State by Ultrasound


ULTRASONIC ACTIVATABLE CONTRAST AGENTS

Before Activation Pulse

After Activation Pulse


ULTRASONIC ACTIVATABLE CONTRAST AGENTS

- Applications
  - Vascular Occlusion
  - Extravascular Diagnostics
  - Other microbubble applications

ULTRASONIC ACTIVATABLE NANOPARTICLES

- Liquid Perfluorocarbon Core
- Lipid or Polymer Shell
- Tipped to Gaseous State by Ultrasound

*Example:*

A Nanoscale Approach to Molecular Imaging

ULTRASONIC ACTIVATABLE NANOPARTICLES

- Liquid Perfluorocarbon Core
- Lipid or Polymer Shell
- Tipped to Gaseous State by Ultrasound

Example:

ULTRASOUND BIOEFFECTS AND THERAPY

BIOLOGICAL EFFECTS – INTERACTION BETWEEN ULTRASOUND AND MICROBUBBLES

- Increased thermal energy conversion
- Physical effects from bubbles themselves
  - Microstreaming
  - Mechanical stimulation of biological membranes
- Cavitation (violent expand/collapse)
  - Shock Waves
  - Microbubble Jetting
  - High Pressures and Temperatures
  - Free Radical Formation
BIOLOGICAL EFFECTS

Mild
• Reversible Capillary Permeability Changes
• Reversible Cell Membrane Permeability
• Small temperature changes

Strong
• Capillary Rupture
• Tissue ablation
• Cell death


BIOLOGICAL EFFECTS

• Occur at low frequencies (~1 MHz) below that typically used for clinical imaging
• Occur at ultrasound intensity levels greater than that typically used for clinical imaging

BIOEFFECTS USED THERAPEUTICALLY

• Drug delivery – can be achieved LOCALLY with focused ultrasound and microbubbles
• Enhanced blood brain barrier permeability
• Enhanced capillary permeability
• Increased cellular delivery through cell membrane permeability
• Have been shown to significantly enhance local drug and gene delivery, and corresponding therapeutic response
• Improved thermal ablation (requires less delivered power with microbubbles – reduces thermal damage to healthy tissues)
EXAMPLE: TRANSIENT BLOOD BRAIN BARRIER OPENING


SAFETY

MICROBUBBLE CLEARANCE

- Microbubbles are vascular agents
- Phagocytosis in Liver and Spleen
- Gas is expelled through the lungs
- Shell content is eliminated by kidney and liver
- Phospholipids enter normal metabolism
- Typical circulation half life ~ 5-15 minutes

SAFETY CONCERNS

- 1994 Albunex (albumin shell – air core)
- 1997 Optison (albumin shell – perfluorocarbon core)
- 2001 Definity (lipid shell – perfluorocarbon core)

Did not administer DEFINITY® to patients with known or suspected right-to-left, bidirectional or reverse-right-to-left cardiac shunts, by ventriculography, or to patients with known hypersensitivity to perfluorocarbons.

Following reports of 11 deaths and 199 serious cardiopulmonary reactions after the administration of such agents in echocardiography.

2007: Black box Warning

Class label changes for ultrasound contrast agents:
- Contraindications for patients with serious cardiopulmonary conditions
- Black WARNING
- Mandatory physiologic monitoring

WARNING: Serious Cardiopulmonary Reactions
Serious cardiopulmonary reactions, including fatalities, have occurred during or following perfusions containing microbubble administrations.

- 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 signs, measurements, electrocardiogram, and respiratory oxygen saturation during and for at least 30 minutes after DEFINITY® administration (see WARNING).
- Always have resuscitation equipment and trained personnel readily available.
SAFETY CONCERNS

- Extensive Investigative Studies
- > 5 million administered doses
  - Most frequent adverse reactions are mild
  - Headache: 5%, Nausea 4%, Flushing 4%, Dizziness 3%.
  - Arrhythmias, hyper/hypotension, neurologic and anaphylactoid reactions - rare

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Severe adverse effects</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contrast Echo</td>
<td>Death</td>
<td>1:500,000</td>
</tr>
<tr>
<td>Pericardial contrast</td>
<td>Anaphylactic reaction</td>
<td>1:10,000</td>
</tr>
<tr>
<td>Exercise ECG</td>
<td>MI/Death</td>
<td>1:2,000</td>
</tr>
<tr>
<td>Dobutamine stress test</td>
<td>MI/VF</td>
<td>1:2,000</td>
</tr>
<tr>
<td>Coronary angiography</td>
<td>Death</td>
<td>1:1,000</td>
</tr>
<tr>
<td>Iodine (CT) contrast exam</td>
<td>Life-threatening reaction</td>
<td>1:500 – 1:5000</td>
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Table modified from Main et al. JACC 2007;50:2434-7 and from www.ICUS-society.org

FDA Revised Contrast Agents Labeling in Oct 2011

- SAFETY OF ULTRASOUND CONTRAST AGENTS:
  - Summary
    - Ultrasound contrast agents are very safe with a low incidence of side effects
    - They are not nephrotoxic or cardiotoxic
    - Incidence of hypersensitivity or allergic events appears much lower than current X-ray or MR contrast agents
    - As in all clinical procedures, physicians should balance potential clinical benefit against the theoretical possibility of associated adverse biologic effects in humans
    - New accreditation standards (ICAEL) for the first time require US echocardiography laboratories to use ultrasonic contrast agents to improve suboptimal echocardiograms, unless an alternative imaging plan is in place
    - Cardiologists and radiologists throughout Europe, Canada, Asia and Latin America routinely and safely use CEUS to image and diagnose abnormalities throughout the body as well as tumors of the liver, ovaries, breast, testicles, lymph nodes, etc.
QUESTIONS?