BASIC PHYSICS AND SAFETY OF CONTRAST MICROBUBBLES

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Acknowledgements

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Disclosures

- Equipment loan from Canon Medical Systems
- Equipment loan from GE Medical Systems
- Equipment loan from Siemens Healthineers
- Contrast agent from GE Healthcare
- Contrast agent from Lantheus Medical Imaging
- Contrast agent from Bracco

Ultrasound Contrast Agents

- Gas filled 1 to 10 μm bubbles
- Air or higher molecular weight gasses
- Bubbles are encapsulated for longevity
  - Albumin or polymer hard shell
  - Lipid or surfactant coated
- Injected intravenously and circulate systemically
- Up to 30 dB increase in SNR
- Signals mainly from vessels 20 - 40 μm

FDA Approved Contrast Agents

<table>
<thead>
<tr>
<th>Name &amp; manufacturer</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optison</td>
<td>LVO &amp; EBD</td>
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<tr>
<td>GE Healthcare, NJ</td>
<td></td>
</tr>
<tr>
<td>Definity</td>
<td>LVO &amp; EBD</td>
</tr>
<tr>
<td>Lantheus Medical, MA</td>
<td></td>
</tr>
<tr>
<td>Lumason (SonoVue)</td>
<td>LVO &amp; EBD</td>
</tr>
<tr>
<td>Bracco, Milan, Italy</td>
<td>focal liver lesions</td>
</tr>
<tr>
<td></td>
<td>vesicoureteral reflux</td>
</tr>
</tbody>
</table>

Microbubble Oscillations

- compression
- expansion

Nonlinear Contrast Spectrum

Harmonic Imaging (HI)
Frequency response of the transducer and the beamformer

Tissue Mimicking Phantom

HI Basics
- Almost no harmonics generated in near field
  - Near field artifact is suppressed
- Main beam is much stronger than the sidelobes
  - Sidelobe artifact is preferentially suppressed
- Harmonic only goes through tissue once
  - Attenuation effects are somewhat limited

Contrast Imaging Modes

Contrast Imaging Modes
Contrast Imaging Modes

**high acoustic power**
- Relies on destruction to differentiate bubbles from tissue
- Requires low frame rate or sweep through tissue
- Examples:
  - Agent Selection Imaging (MRI)
  - Coded Harmonic Angio (CHA)
  - Color overlay (AE, ADF, …)

**low acoustic power**
- Images stable harmonics from bubbles, reduced tissue nonlinearities
- Real time imaging, but with reduced penetration
- Examples:
  - Pulse Inversion
  - Cadence Pulse Sequence (CPS)
  - Subtract & integrate (MVI, MFI)

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Pulse Inversion Imaging

<table>
<thead>
<tr>
<th>Linear scattering</th>
<th>[p_0(t)]</th>
<th>Echo_1</th>
</tr>
</thead>
<tbody>
<tr>
<td>[p_1(t)]</td>
<td>Echo_1 + Echo_2</td>
<td></td>
</tr>
</tbody>
</table>

Liver Lesion Characterization

- Diagnostic: HCC
- 2 minutes
- 3 minutes
- 4 minutes

Low versus High Acoustic Power Techniques

- Most low power techniques also work for high power, but must be optimized differently
  - e.g., Pulse Inversion extracts harmonics well at low MI, but also detects pulse-to-pulse differences at high MI

- Internal system settings are different for low versus high power
  - Turning up the power on a low MI setting may not work as well at high MI as one that is optimized for high MI by the manufacturer
  - Turning down the power on a high MI setting probably won't work at all at low MI

Microbubble Fragmentation

(1 cycle, 2.4 MHz at 1.1 MPa)
Destruction Replenishment Method

In Vivo Perfusion Measurement

Capillary/Slow Flow Imaging

Normal Testicle

International Guidelines

10+ Years of Black Box Warnings for UCAs
FDA Black Box Warning

- Issued in October 2007 and highlighting the risk of "serious cardiopulmonary reactions" within 30 minutes of administration of either Definity or Optison
- Spontaneous healthcare provider reports of several patient deaths (4) and approximately 190 "severe cardiopulmonary reactions" which occurred in close temporal relationship to UCA injection, or other conditions that cause cardiopulmonary symptoms
- Epidemiologic type study performed by FDA to determine "risk factors" for adverse reactions; mandated 30 minute monitoring period following UCA administration in all patients

Results

- 26 deaths for Definity
- 66 deaths for Non-Contrast

No difference in 24 hour mortality in hospitalized patients undergoing echocardiography with or without contrast administration

Meta-Analysis of Mortality Associated with UCAs

![Meta-Analysis of Mortality Associated with UCAs](image)

- 19,671 patients
  - 12,475 unenhanced
  - 6,196 Definity
- In-patient echocardiography between January 2005 and October 2007
- Vital status at 24 hours available for all patients

History of Product Label Changes

![History of Product Label Changes](image)

- Multiple product label changes
- 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 UCA administration in all patients
Recent FDA UCA Label Changes

In October 2016, the FDA rescinded the shunt contra-indication for Optison and more recently for Lumason and Definity.

However, the following was added to the Warnings and Precautions portion of the product label:

“When administering Optison to patients with a cardiac shunt, microspheres can bypass filtering of the lungs and enter the arterial circulation. Assess patients with shunts for embolic phenomena after Optison administration.”

[Reference: Muskula & Main, Circ Cardiovasc Imaging, 2017]

Event Rates for Commonly Performed Cardiovascular Procedures

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Event Rate</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary Angiography</td>
<td>1:1000</td>
<td>Death</td>
</tr>
<tr>
<td>Exercise Treadmill Testing</td>
<td>1:2500</td>
<td>MI or Death</td>
</tr>
<tr>
<td>SPECT Exam or Radiouclide Ventriculography</td>
<td>1:1000 to 1:10,000</td>
<td>Fatal Malignancy</td>
</tr>
<tr>
<td>Contrast Echocardiography</td>
<td>1:500,000</td>
<td>Death</td>
</tr>
</tbody>
</table>

Contrast Echocardiography as a Percentage of Total Echocardiography

[Graph showing Contrast Echocardiography as a Percentage of Total Echocardiography through June 2017]

Contrast imaging techniques can be divided into two groups:

- **High acoustic power**: very sensitive, but transient
- **Low acoustic power**: less sensitive, but real-time

Multi-pulse detection schemes can suppress linear signals and enhance nonlinear signals

UCAs are “safe” and their use improves outcomes in patients with baseline technically difficult studies

There is an approximate 1:10,000 risk of an anaphylactoid reaction

The FDA’s own internal guidelines suggest the Black Box warning is not supported for UCAs that are associated with rare, idiosyncratic AEs

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Resources

- FDA: [https://www.fda.gov/](https://www.fda.gov/)
THANK YOU!