Mechanisms and role of contrast echocardiography

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Contrast echocardiography is a variety of techniques whereby the blood pool on cardiac ultrasound is enhanced with encapsulated gas-filled microbubbles or other acoustically active nano- or microparticles.
Right Heart Contrast Echo

- Agitated saline
- Bubble diameter is greater than diameter of pulmonary capillaries
- No transpulmonary passage (in absence of intrapulmonary shunt)
- PFO/ASD/Persistent Left Superior Vena Cava
Ultrasound contrast agents

- Encapsulated microbubbles with albumin or lipid shell
- 2-5 um in diameter
- Stability enhanced by high-molecular weight gas
- Signal produced by their volumetric oscillation in an ultrasound field
- Special “bubble-specific” imaging presets available.

Image courtesy of Jonathan R. Lindner
Bubble compression and expansion occur during different pressure phases of the acoustic wave, shown schematically by the location of frames a–e.
Ultrasound contrast agents

Microbubbles are not just passive reflectors but active generators of sound energy.

1. **High echogenecity**: strong ultrasound reflectors
2. **Linear relationship** between concentration and signal intensity
3. **Ability to cross the pulmonary capillary bed** (< 5μm)
4. **Stability** over the duration of the procedure
5. **Safety**: Non toxicity
6. Minimal imaging artifacts
7. **Special properties** (e.g. site-specific therapeutic drug delivery)
Contrast agents for ultrasound

- **The first generation agents**: air bubbles stabilized by encapsulation (Albunex) or by adherence to microparticles (Levovist).

- **The second generation agents**: replacing air with a low solubility fluorocarbon gas stabilizes bubbles still further example, Definity, Sonazoid, Optison, SonoVue, greatly increasing the duration of the contrast effect.

- **Third generation agents**: use polymer shell and low solubility gas and should produce much more reproducible acoustic properties.

**Table 1. Example of commercially-produced microbubble contrast agents**

<table>
<thead>
<tr>
<th>Shell</th>
<th>Gas</th>
<th>Size (μm)</th>
<th>Proprietary name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid</td>
<td>C₄F₁₀</td>
<td>1–3</td>
<td>Definity</td>
</tr>
<tr>
<td>Lipid</td>
<td>C₄F₁₀α</td>
<td>2</td>
<td>Sonazoid</td>
</tr>
<tr>
<td>Lipid</td>
<td>SF₆</td>
<td>2–3</td>
<td>Sonovue</td>
</tr>
<tr>
<td>Lipid</td>
<td>Air</td>
<td>2–3</td>
<td>Levovist</td>
</tr>
<tr>
<td>Lipid</td>
<td>C₃F₈</td>
<td>2–4</td>
<td>Optison</td>
</tr>
<tr>
<td>Albumin</td>
<td>Air</td>
<td>2–3</td>
<td>AI-700</td>
</tr>
<tr>
<td>Polymer (PLGA)</td>
<td>PFC</td>
<td>2–3</td>
<td>Cardiosphere</td>
</tr>
<tr>
<td>Polymer/albamin</td>
<td>Air</td>
<td>2–3</td>
<td></td>
</tr>
</tbody>
</table>

PFC: perfluorocarbon gas (not disclosed), PLGA: polylactide co-glycolate

Nonlinear response of the microbubble
# Imaging Modalities

<table>
<thead>
<tr>
<th>Power MI</th>
<th>Type of imaging</th>
<th>Technology</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (0.8–1.0)</td>
<td>Intermittent</td>
<td>Power Doppler ultraharmonics</td>
<td>Very sensitive for detection of contrast</td>
<td>Cannot assess wall motion simultaneously</td>
</tr>
<tr>
<td>Low (0.1–0.3)</td>
<td>Continuous (real time)</td>
<td>Power modulation</td>
<td>Wall motion can be assessed simultaneously</td>
<td>Less sensitive for detection of contrast</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Power pulse inversion</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cadence pulse sequencing (or coherent contrast imaging)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**Triggered Replenishment Imaging**

- **ECG**
- **Flash**

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*European Journal of Echocardiography 2009; 10: 94–212*
Perfusion imaging

the passage of contrast agent through blood vessels to an organ or a tissue

Molecular imaging

the expression of relevant disease-specific molecules (site-targeted)
Microvascular Behavior of microbubbles

Images and video courtesy of Dr Jonathan R. Lindner.
Perfusion Imaging

Destruction - replenishment Kinetics

Post-destruction

- 50 ms
- 1 s
- 10 s
PI versus myocardial VI relation

can be fitted to an exponential function

\[ y = A(1 - e^{-\beta t}) \]

- \( y \) is myocardial VI at a PI of \( t \)
- \( A \) is the plateau VI representing MBV
- \( \beta \) is the rate constant representing the mean myocardial blood flow velocity from the slope of the time-intensity curve

A×\( \beta \)= Blood flow

Wei K. et. Al. circulation. 1988
Myocardial blood flow quantification with contrast echocardiography

1. Visual analysis
2. Myocardial blood volume quantification
3. Parametric imaging
1. **Visual analysis**, which is semi-quantitative, subjective, limited to the observer’s experience.
2. **Myocardial blood volume quantification**, and of the myocardial blood flow velocity in regions of interest (ROI) in the myocardium, using a specific computer program.
3. **Parametric imaging**, a novel method of automated quantification in which the myocardial blood flow is codified in colors all over the myocardium, according to the degree of perfusion: **green** (normal perfusion), **yellow** (moderate decreased), **red** (severe decreased)
Left ventricular opacification
The clinical applications of CAD

1. Assessment of patients with suspected or known coronary artery disease

2. Determination of the area at risk and efficacy of reperfusion therapies in patients with AMI

3. Assessment of myocardial viability after infarction (no-reflow phenomenon)
Coronary circulation

Myocardial contrast enhancement represents the primarily the capillary blood volume
M/ 67, Chest pain

Images courtesy of Kim Hyung-Seop
Apical 2 chamber view

**Resting**

**Stress - adenosine**

Images courtesy of Kim Hyung-Seop
Images courtesy of Kim Hyung-Seop
Comparative Accuracy of Real-Time MCE and WM Analysis During Dobutamine Stress Echo for the Diagnosis of CAD

170 patients who underwent dobutamine-atropine stress testing and CAG.

LAD and LCX disease.
Pooled regional sensitivities of wall motion analysis and MCE for the diagnosis of coronary stenoses

J Am Coll Cardiol 2004;44:2185–91
MCE for the Detection of CAS: A Prospective Study in Comparison With SPECT

123 patients scheduled for CAG underwent MCE and SPECT imaging at rest and after vasodilator stress.
Comparison of MCE and SPECT in the detection of CAD

Myocardial contrast echocardiography; MCE

Myocardial contrast echocardiography vs SPECT for different degrees of stenosis:
- ≥50% stenosis:
  - Sensitivity: MCE 84%, SPECT 87%
  - Specificity: MCE 82%, SPECT 86%
- ≥70% stenosis:
  - Sensitivity: MCE 56%, SPECT 50%
  - Specificity: MCE 52%, SPECT 50%
- ≥90% stenosis:
  - Sensitivity: MCE 40%, SPECT 89%
  - Specificity: MCE 40%, SPECT 88%

J Am Coll Cardiol 2006;47:141–5
The detection of coronary artery disease in the posterior circulation was studied using myocardial contrast echocardiography and SPECT imaging.

**Anterior circulation**

- Sensitivity: 56% for ≥50% stenosis, 81% for ≥70% stenosis, 79% for ≥90% stenosis
- Specificity: 49% for ≥50% stenosis, 83% for ≥70% stenosis, 82% for ≥90% stenosis

**Posterior circulation**

- Sensitivity: 71% for ≥50% stenosis, 72% for ≥70% stenosis, 78% for ≥90% stenosis
- Specificity: 68% for ≥50% stenosis, 61% for ≥70% stenosis, 80% for ≥90% stenosis

*Source: J Am Coll Cardiol 2006;47:141–5*
Assessment of myocardial collateral blood flow

Post-mortem high-resolution angiogram the heart

Normal

LAD occlusion

From Gross and Kugel with permission from C.V. Mosby Company.
A patient with occluded RCA after AMI

A MCE image after microbubble injection into the left main coronary artery

After successful angioplasty of the RCA and direct injection of microbubble

Perfusion defect size at various times after bubble destruction and final infarct size

A dog undergoing 6 hours of LCX occlusion.

Rich collateral-derived flow

Poor collateral-derived flow

Determination of Size and Transmural Extent of AMI by Real-time MPE: A Comparison with MRI

20 patients underwent MPE and MRI between the 2nd and 5th day post-AMI.

PI: parametric imaging
Pearson’s and Bland Altman correlation between average infarct area by measurement using gray and parametric imaging

\[ y = 1.5042x + 0.2341 \]
\[ R = 0.82 \]
\[ p < 0.001 \]

\[ y = 1.3597x - 0.0039 \]
\[ R = 0.92 \]
\[ p < 0.001 \]
Relation of wall-motion score determined by echo and mean transmural extent of AMI
Regional LV perfusion and function in patients presenting to the emergency department with chest pain and no ST elevation

- 1017 patients
- Routine evaluation: Demographics, Clinical, EKG, RF and MP using contrast echocardiography
- Early (48h) event: Cardiac-related death, AMI, unstable angina, CHF, and revascularization
Incremental value of tests performed for prediction of events

**Early events**

D, demographics; C, clinical; E, EKG. RF: regional function, MP: myocardial perfusion. P-values as Bonferroni corrected

Events within 48 h (early): Cardiac-related death, acute myocardial infarction, unstable angina pectoris, congestive heart failure (CHF), and revascularization

-European Heart Journal 2005: 26; 1606–11-
Survival probabilities - Different combinations of RF and MP values

The survival probabilities have been adjusted for patients’ age, hypertension, diabetes, hypercholesterolaemia, smoking status, and EKG.

European Heart Journal 2005: 26; 1606–11
Intravenous MCE Predicts Recovery of Dysynergic Myocardium Early After AMI

- 96 patients with recent AMI underwent echocardiography at baseline and six months later or three months after revascularization.
- MCE: baseline using intravenous injections of Optison. Triggering intervals of 1:1 (early) and 1:10 (delayed) cardiac cycles.
- Viable segments: homogeneous contrast opacification.

- Independent predictors of functional recovery were delayed MCE (odds ratio [OR]: 4.0, p < 0.001), revascularization (OR: 6.0, p < 0.001), and log creatine kinase (OR: 0.5, p < 0.03).
Intravenous delayed triggered MCE can independently detect myocardial viability early after AMI.
1. Molecular Imaging of Vascular Inflammation in Atherosclerosis

2. Ischemic memory: detect the residual signature of prior myocardial ischemia without infarction

3. Drug and gene delivery: vascular endothelial growth factor (VEGF) and stem cell factor (SCF)
Conclusions

1. Contrast echocardiography is a portable real-time, safe method.

2. It significantly improves the image quality during rest and stress, provides information on myocardial perfusion.

3. While MCE perfusion imaging for assessment of CAD is not yet mainstream, there are still niche applications where the assessment of perfusion with microbubbles has a high impact.