Myocardial Contrast Echo

Anthony DeMaria

Myocardial Contrast Echocardiography: Problems and Potential

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Immedicate Past Editor, JACC

Grantee, SAB, Sponsored Speaker,
Ad hoc Consultant
Virtually All Ultrasound Instrument and Contrast Companies
CONTRAST ECHO

- Effective contrast agents
- Refined recording techniques
- LV cavity opacification
- Doppler enhancement
- Myocardial perfusion
- Delivery of markers, drugs, therapy

Contrast for LV Opacification
LV Opacification Echo Other Than Border Definition

- Cardiac Shunts
- Doppler enhancement
- Cardiac Masses
  - Tumor vs Clot
- 3D enhancement
- Noncompaction
- Vascular enhancement

Proverb

‘It is dangerous to have great potential for too long a time.’
Applications of MCE in CAD

- Risk area or infarct size with MI
- Reperfusion efficacy
- No-reflow phenomenon
- Myocardial viability
- Coronary collateral flow
- Coronary artery stenosis
- Coronary flow reserve
- Targeted marker or drug delivery

Myocardial contrast echocardiography has not yet achieved use as a clinical tool.

Why?
Ultrasound contrast agents have been very difficult to successfully develop and market

Microbubble Properties: *Shell and Gas*
### Contrast Agent Properties

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mean Size (u)</th>
<th>Gas</th>
<th>Shell</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levovist</td>
<td>2-3</td>
<td>Air</td>
<td>(Galactose)</td>
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<tr>
<td>Optison</td>
<td>4.7</td>
<td>Perfluoropropane</td>
<td>albumin</td>
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<tr>
<td>Definity</td>
<td>1.5</td>
<td>Perfluoropropane</td>
<td>phospholipid</td>
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<tr>
<td>Imagent</td>
<td>5.0</td>
<td>Perfluorohexane-N</td>
<td>Surfactant</td>
</tr>
<tr>
<td>Lumason (Sonovue)</td>
<td>2.5</td>
<td>Sulfur hexafluoride</td>
<td>Phospholipid</td>
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<tr>
<td>Cardiosphere</td>
<td>4.0</td>
<td>Nitrogen</td>
<td>Polymer</td>
</tr>
<tr>
<td>Acusphere</td>
<td>2.0</td>
<td>Perfluorocarbon</td>
<td>Polymer</td>
</tr>
</tbody>
</table>

### Contrast Recording Techniques

- **Destructive**  
  - *high energy*, unipulse  
  - Most sensitive  
  - Triggered, no motion  
  - Can get tissue signals  
  - Power Doppler  
  - Ultraharmonics

- **Non-destructive**  
  - *low energy*, multipulse  
  - Real-time, motion  
  - Ease of use  
  - Less sensitivity  
  - Non-linearity methods  
  - Pulse inversion  
  - Power modulation  
  - Coherent imaging
Contrast Echo is not Contrast

• White blood volume signal superimposed upon white tissue

• Techniques needed to differentiate microbubbles from tissue
  • ECG gating
  • Harmonics
  • Non-linear signals
  • Bubble destruction (refill imaging)

Bubbles Produce Harmonic Signals

Fig. 4 (a) Characteristic harmonic spectrum from a sample of nonlinear contrast agent. Experimental parameters are described in the text. (b) Spectrum generated from test cell filled only with distilled water, taken under the same conditions as in (a). Note different vertical scales.
Interaction of Ultrasound and Microbubbles

**Linear resonance**
- Fundamental enhancement

**Nonlinear resonance**
- Harmonic enhancement

**Transient scattering**
- Bubble disruption

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

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*Wei et al., Circ. 97:1998*
Contrast perfusion defects are time dependent
Averaged Values of Myocardial Signal Intensity

Signal Intensity (dB)

Time (Frames After “FLASH”)

No stenosis
Mild-NFLS
Moderate-NFLS
Severe-NFLS
FLS
Occlusion

Masugata et al. Circ: 2002

Baseline
### Refilling Sequence All Frames Adenosine

![Image](image-url)

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Pts</th>
<th>MCE Mode</th>
<th>Stress Method</th>
<th>Criterion Standard</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Concordance</th>
<th>Kappa</th>
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<tbody>
<tr>
<td>Kaul</td>
<td>1997</td>
<td>30</td>
<td>High MI</td>
<td>dipyridamole</td>
<td>SPECT</td>
<td>-</td>
<td>86%</td>
<td>-</td>
<td>0.71</td>
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<tr>
<td>Porter</td>
<td>1997</td>
<td>28</td>
<td>High MI</td>
<td>dipyridamole</td>
<td>SPECT</td>
<td>92%</td>
<td>84%</td>
<td>84%</td>
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<tr>
<td>Heinle</td>
<td>2000</td>
<td>123</td>
<td>High MI</td>
<td>adenosine</td>
<td>SPECT</td>
<td>-</td>
<td>81%</td>
<td>-</td>
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<tr>
<td>Cwajg</td>
<td>2000</td>
<td>45</td>
<td>Low MI</td>
<td>exercise/dipyridamole</td>
<td>Angiography</td>
<td>-</td>
<td>80%</td>
<td>80%</td>
<td>0.61</td>
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<tr>
<td>Shimoni</td>
<td>2001</td>
<td>100</td>
<td>low MI</td>
<td>exercise</td>
<td>SPECT</td>
<td>-</td>
<td>76%</td>
<td>-</td>
<td>0.50</td>
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<tr>
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<td>2001</td>
<td>44</td>
<td>low MI</td>
<td>exercise</td>
<td>Angiography</td>
<td>75%</td>
<td>100%</td>
<td>-</td>
<td>0.67</td>
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<tr>
<td>Porter</td>
<td>2001</td>
<td>117</td>
<td>low MI</td>
<td>dobutamine</td>
<td>dobutamine stress echocardiogram</td>
<td>-</td>
<td>91%</td>
<td>-</td>
<td>0.70</td>
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<tr>
<td>Porter</td>
<td>2001</td>
<td>40</td>
<td>low MI</td>
<td>dobutamine</td>
<td>Angiography</td>
<td>-</td>
<td>83%</td>
<td>83%</td>
<td>0.65</td>
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<tr>
<td>Oraby</td>
<td>2001</td>
<td>27</td>
<td>high MI</td>
<td>dobutamine</td>
<td>SPECT</td>
<td>-</td>
<td>82%</td>
<td>-</td>
<td>0.40</td>
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<tr>
<td>Haluska</td>
<td>2001</td>
<td>49</td>
<td>high MI</td>
<td>dobutamine</td>
<td>SPECT</td>
<td>83%</td>
<td>55%</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Wei</td>
<td>2003</td>
<td>43</td>
<td>high MI</td>
<td>dobutamine</td>
<td>SPECT</td>
<td>96%</td>
<td>63%</td>
<td>84%</td>
<td>0.63</td>
</tr>
</tbody>
</table>

### Detection of Myocardial Ischemia/Coronary Stenosis by MCE

![Image](image-url)
Detection of coronary artery disease with perfusion stress echocardiography using a novel ultrasound imaging agent: two Phase 3 international trials in comparison with radionuclide perfusion imaging

RAMP 1 and 2
Real time assessment of myocardial perfusion

• Imagify is perflubutane polymer microspheres (poly-D,L-lactide-co glycolide and phospholipid)

• Used both real-time and gated ultraharmonic imaging

• Core laboratories for all images
  • 3 echo and 1 nuclear reader compared

• Stenosis as 70% and global jeopardy score

• 652 pts enrolled; approximately 53% CAD

• Non-inferiority design
Al 700 Dipyridamole

![Image of ultrasound scan]

Al 700 Dipyridamole

![Image of another ultrasound scan]
RAMP 1 and 2

ROC Analysis: RAMP 1 and 2

Senior et al: Eur J Echo; 2009
MCE vs Spect

- 513 pts with known or suspected CAD
- Sulphur hexafluoride continuous infusion
- Dipyridamole stress with destroy/refill
- SPECT and cor angio in standard fashion
- 3 expert readers for each: collapsed into 1
- MCE + if no stress refill by after 4 cycles
- SPECT by visual assessment
- Non-inferiority design
Diagnostic Accuracy: MCE vs SPECT

Senior et al; JACC, 2013

ROC Analysis: MCE vs SPECT

Senior et al; JACC, 2013
### Viability by MCE

<table>
<thead>
<tr>
<th>Authors</th>
<th>Imaging type</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Janardhanan (2005)</td>
<td>Low MI</td>
<td>82</td>
<td>83</td>
<td>42</td>
</tr>
<tr>
<td>Hickman (2005)</td>
<td>Low MI</td>
<td>83</td>
<td>78</td>
<td>56</td>
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<tr>
<td>Senior (2003)</td>
<td>High MI</td>
<td>62</td>
<td>85</td>
<td>96</td>
</tr>
<tr>
<td>Greavea (2003)</td>
<td>Low MI</td>
<td>88</td>
<td>74</td>
<td>15</td>
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<tr>
<td>Aggeli (2003)</td>
<td>High MI</td>
<td>87</td>
<td>72</td>
<td>34</td>
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<tr>
<td>Janardhanan (2003)</td>
<td>Low MI</td>
<td>92</td>
<td>75</td>
<td>50</td>
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<tr>
<td>Hillia (2003)</td>
<td>Low MI</td>
<td>86</td>
<td>44</td>
<td>33</td>
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<tr>
<td>Hillis (2003)</td>
<td>High MI</td>
<td>80</td>
<td>67</td>
<td>38</td>
</tr>
<tr>
<td>Lepper (2002)</td>
<td>High MI</td>
<td>94</td>
<td>87</td>
<td>35</td>
</tr>
<tr>
<td>Main (2001)</td>
<td>Low MI</td>
<td>77</td>
<td>83</td>
<td>34</td>
</tr>
</tbody>
</table>

**Mean** 83 75 *(n 430)*

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### MCE for Myocardial Viability Post MI

Ragosta et al.; 89:1994
Why is MCE Not Clinical?

- Images still inadequate in difficult patients
- Pulsing sequences still complex
- No agreed upon protocol exists
- Quantitation still has limited reproducibility
- Few multicenter studies are published
- No reimbursement