ROLE OF CONTRAST AGENTS TO ENHANCE WALL MOTION AND DOPPLER SIGNALS

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Disclosure

- Monthly Echo conference lunch by Sonovue distributor
2 Components of Contrast Echo

UCA $\rightarrow$ UEA

(ultrasound contrast $\rightarrow$ enhancing agents)

Ultrasound waves
(System Technologies)

- Air
- Gas
- Liquid

Shell:
- Protein
- Lipid
- Surfactant
- Polymer

- Size: 1-8 μ
- Biodegradable
- Scatter US
Bubbles oscillate non-linearly. Myocardium oscillate linearly.

When insonicated, bubbles emit non-linear acoustic signals of varying harmonics.

**CE aim to enhance non-linear signals from bubbles while suppressing linear signals (noise) from myocardium**, i.e. increase signal to noise ratio.
## Approved 2nd Generation Microbubbles

### Table 1: Currently marketed ultrasound contrast agents.

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Manufacturer</th>
<th>Year approved</th>
<th>Inner gas</th>
<th>Outer shell</th>
<th>Approved for</th>
<th>Marketed in</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optison</td>
<td>GE Healthcare Lantheus Medical Imaging</td>
<td>1997</td>
<td>Perfluorhexane</td>
<td>Albumin</td>
<td>LVO/EBD</td>
<td>USA, Europe, Canada, North America, New Zealand, Europe, Brazil, parts of Asia</td>
</tr>
<tr>
<td>Definity/Luminary</td>
<td>Lantheus Medical Imaging</td>
<td>2001/2006</td>
<td>Perfluorhexane</td>
<td>Lipid</td>
<td>LVO/EBD, Liver</td>
<td>USA, Europe, Canada, North America, New Zealand, Europe, Brazil, parts of Asia</td>
</tr>
<tr>
<td>Sonovue/Lumason</td>
<td>Bracco Imaging S.p.A</td>
<td>2001/2014</td>
<td>Sulfur hexafluoride</td>
<td>Lipid</td>
<td>LVO/EBD, Breast</td>
<td>North America, New Zealand, Europe, Brazil, parts of Asia</td>
</tr>
<tr>
<td>Sonazoid</td>
<td>GE Healthcare</td>
<td>2007</td>
<td>Perfluorbutane</td>
<td>Lipid</td>
<td>Liver, Breast</td>
<td>Japan, South Korea</td>
</tr>
</tbody>
</table>

LVO, left ventricular opacification; EBD, endocardial border definition; DAV, diagnostic assessment of vessels.

*Only in certain countries.

- **FDA approved** – Lumason, Definity and Optison
- **Europe EMA approved** – Sonovue (Lumason)
- **Singapore HSA approved** – Definity, Sonovue
Choice of Imaging modality for LVO:
B mode low MI harmonic or Very Low MI (VLMI)

VLMI (very low MI < 0.2) imaging is preferred

- better tissue cancellation increased sensitivity for detecting bubble signals
- greater signal to noise ratio
- Less bubble destruction
- Allows simultaneous assessment of RWM and perfusion

Various mode of VLMI – power modulation, pulse inversion, pulse sequencing
Indications for UEAs (Ultrasound Enhancing Agents)

1. Left Ventricular Opacification (LVO)
   - FDA approved

2. Myocardial Perfusion Echocardiography (MCE)
   - Off label

3. Sonoporation - Targeted drug and gene delivery
   - Research
Indications for LVO

1. For endocardial border definition (EBD) to provide an accurate assessment and/or quantification of RWM, LVEF and LV volumes

2. Enhancement of left and right-sided Doppler signals, when UEAs are being used for other imaging indications.

3. To confirm or exclude LV structural abnormalities
Clinical Applications of Ultrasonic Enhancing Agents in Echocardiography: 2018 American Society of Echocardiography Guidelines Update

Key Points and Recommendations

1. As per 2008 ASE guidelines, for routine resting echocardiographic studies, UEAs should be used when two or more LV segments cannot be visualized adequately for the assessment of LV function (LVEF and RWM assessment) and/or in settings in which the study indication requires accurate analysis of RWM (COR 1, LOE A).

2. A brief (5- to 10-frame) high-MI (≥5.5) imaging to clear myocardium of contrast is performed for volume and ejection fraction (EF)

3. Ultrasound enhancement should be considered for the enhancement of LVEF is important to provide accurate measurements of LVEF and low-MI harmonic imaging (VLMI) is required (COR I, LOE B-R).

4. LV volumes obtained by enhancement should be measured without UEAs, and the calculation of volumes should be applied with caution. Use of a normal range for LVEF does not correlate with the end-diastolic and end-systolic LV volumes.

5. As per section III of the 2014 ASE recommendations, a low volume (≤0.5 mL) enhancement is recommended along with VLMI and basal segment attenuation.

- 5-15% of patients and up to 30% of ICU patients due to obesity, lung diseases, mechanical ventilation or chest deformities.
60 yr Obese DM gentleman admitted for heart failure

Unenhanced echo

B mode 2\textsuperscript{nd} harmonic low MI imaging
Subjectivity of RWM interpretation

Analysis of Regional Left Ventricular Function by Cineventriculography, Cardiac Magnetic Resonance Imaging, and Unenhanced and Contrast-Enhanced Echocardiography

A Multicenter Comparison of Methods

Rainer Hoffmann, MD,* Stephan von Bardeleben, MD,† Jaroslaw D. Kasprowski, MD,‡ Adrian C. Borges, MD,§ Folkert ten Cate, MD,¶ Christian Fischke, MD, FACC,‖ Stephane Laffitte, MD,§ Nidal Al-Saadi, MD,¶ Stefanie Kuntz-Hehner, MD,‡ Georg Horstick, MD,‡ Christian Greis,‡ Marc Engelhardt, MD,§§ Jean Louis Vanoverschelde, MD, FACC,¶¶ Harald Becher, MD‖

Table 6: Diagnostic Accuracy of Each Imaging Method (Mean From All Three Readers) to Detect the Presence of Regional Wall Motion Abnormalities Defined by a Panel Decision

<table>
<thead>
<tr>
<th></th>
<th>Echo Unenhanced</th>
<th>Echo Contrast Enhanced</th>
<th>Cineventriculography</th>
<th>cMRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>56</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>85.7%</td>
<td>90.2%</td>
<td>86.5%</td>
<td>90.8%</td>
</tr>
<tr>
<td>Specificity</td>
<td>77.3%</td>
<td>81.3%</td>
<td>75.0%</td>
<td>74.4%</td>
</tr>
<tr>
<td>Accuracy</td>
<td>82.9%</td>
<td>87.2%</td>
<td>82.8%</td>
<td>84.9%</td>
</tr>
<tr>
<td>Only cMRI patients</td>
<td>56</td>
<td>56</td>
<td>56</td>
<td>56</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>83.3%</td>
<td>90.7%</td>
<td>84.1%</td>
<td>90.8%</td>
</tr>
<tr>
<td>Specificity</td>
<td>75.0%</td>
<td>83.8%</td>
<td>69.4%</td>
<td>74.4%</td>
</tr>
<tr>
<td>Accuracy</td>
<td>79.5%</td>
<td>88.2%*</td>
<td>78.7%</td>
<td>84.9%</td>
</tr>
</tbody>
</table>

*p = 0.018 vs. echo unenhanced; p = 0.018 vs. cineventriculography.

Accuracy to detect RWMA is highest amongst CE (kappa coefficient 0.77), followed by CMR (0.43), unenhanced echo and cineventriculography.

.. RWMA ..still considerable interobserver variability even with high quality imaging modality..
Impact of Contrast Echocardiography on Evaluation of Ventricular Function and Clinical Management in a Large Prospective Cohort

Kurt et al J Am Coll Cardiol. 2009;53(9):802-810
A Randomized Cross-Over Study for Evaluation of the Effect of Image Optimization With Contrast on the Diagnostic Accuracy of Dobutamine Echocardiography in Coronary Artery Disease: The OPTIMIZE Trial

J Am Coll Cardiol Img. 2008;1(2):145-152

N = 101 underwent both unenhanced and enhanced DSE 4 hrs apart within 24 hrs

B mode harmonic imaging

Definity

CE improved visualisation of segments at rest and at peak (67 → 96%, p < 0.0001) and increased confidence of interpretation (36% → 74%, p < 0.001)

Greatest impact on accuracy when > 2 segments not visualised
Contrast use in patients with suboptimal images improves feasibility and accuracy of stress echo testing. Comparable sensitivity (81% vs 73%, NS) and diagnostic accuracy (82% vs 77% NS) for wall motion analysis compared with patients with optimal image quality.

At long term follow up, abnormal wall motion and/or myocardial perfusion predicted adverse outcomes (20.6%) when compared with normal studies (3.7%).
Contrast-Enhanced DSE predicts hard cardiac events (non-fatal MI and cardiac death) at 3 yrs

Role of Contrast-Enhanced Dobutamine Stress Echocardiography in Predicting Outcome in Patients with Known or Suspected Coronary Artery Disease

Chinami Miyazaki, M.D.,† Shinichiro Otani, M.D.,† Minoru Yoshiyama, M.D., Ph.D.,* and Junichi Yoshikawa, M.D., Ph.D.*

A
Total cardiac events

B
Hard cardiac events

P<0.001

N=893
Levovist
Harmonic imaging

... 3-year event free survival rate was significantly lower in patients with positive DSE results than in those with negative DSE results...

Considering hard cardiac events, the independent predictors were peak WMSI > 1.5 (P<0.0001, HR:6.65) and age>70 years (P < 0.005, HR: 3.27)...

Clinical Applications of Ultrasonic Enhancing Agents in Echocardiography: 2018 American Society of Echocardiography Guidelines Update

Key Points and Recommendations for Stress Echocardiographic Imaging with UEAs

1. UEAs should be used whenever adequate segmental visualization within any coronary artery territory cannot be achieved with resting unenhanced echocardiography (COR I, LOE A).
2. VLMI imaging is the preferred imaging mode for stress echocardiography: high-MI impulses (five to six simultaneous LVO and analysis of RWM motion, continuous 3 to 5 mL/min infusion of Optison) or small bolus injections (1 mL Optison) with slow 5- to 10-mL saline flush and analysis of RWM motion.
3. Continuous 3 to 5 mL/min infusion of Optison or small bolus injections (1 mL Optison) with slow 5- to 10-mL saline flush and analysis of RWM motion.

.. UEAs should be used whenever any segment within any coronary artery territory cannot be adequately visualized...

.. VLMI is preferred imaging mode for RWM analysis at rest and stress in that added perfusion data may help differentiate subtle wall thickening abnormalities due to subendocardial ischaemia.
VLMI imaging improves apical and basal segments visualisation
VLMl allows simultaneous RWM and perfusion assessment during DSE

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RF from CE provides incremental prognostic value in patients presenting to ED with chest pain

**EXPEDITED REVIEW**

Myocardial Contrast Echocardiography Versus Thrombolysis in Myocardial Infarction Score in Patients Presenting to the Emergency Department With Chest Pain and a Nondiagnostic Electrocardiogram

Khim Leng Tong, MD,* Sanjiv Kaul, MD, FACC,* Xin-Qun Wang, MS,† Diana Rinkevich, MD, FACC,* Saul Kalmanits, MD,* Todd Belcik, RDMS,* Wolfgang Lepper, MD,* William A. Foster, MD,*

Kevin Wei, MD, FACC*  
*Charlottesville, Virginia

The mTIMI score was unable to discriminate between intermediate- compared to high-risk patients at any follow-up time point, whereas only 2 of 523 patients with normal RF had an early primary event. Regional function provided incremental prognostic value over mTIMI scores for predicting intermediate and late events. In patients with abnormal RF, MP further classified patients into intermediate- and high-risk groups. The full TIMI score could not improve upon these results at any follow-up time point.
Contrast enhancement of Doppler signals

- When UEAs being used for imaging.
- To enhance TR jet (for RVSP), and peak velocity in valvular stenosis
- Important to reduce Doppler gain to minimize noise and blooming artefact

TR w/o contrast
Vmax = 2.5 m/s

TR with contrast:
Vmax = 3.0 m/s
Aortic Stenosis

AS w/o contrast
PPG = 30 mmHg

AS with contrast
PPG = 70 mmHg
Contrast is cost effective

- Average **cost savings of USD$122 per patient** by reduction of potential downstream testing by 33%. (Kurt et al 2009)
- Potential **savings of USD $238 per patient** with contrast enhanced DSE in suboptimal images from further testing (Thanigaraj et al 2001)

In CGH Singapore -
- 1 vial Sonovue S$150
- Stress echo – S$580
- Stress echo w 1 vial Sonovue - S$730
- MIBI – $995
For optimal wall motion analysis, a good LVO is key

Optimise LVO image
- adjust gain (keep LVO bright and myocardium dark)
- keep attenuation at the mitral level.
- To focus on apex, move focus up to the apex
- Important buttons to note: MI/power, gain, focus
Flush slower
Increase MI to destroy more bubbles

Raise arm, massage veins, increase flush or dose, reduce MI
The saga on safety of UEA

Oct 2007 - FDA “Black Box Warning”
- new contraindications
- mandatory 30 mins monitoring

June 2008 – FDA downgraded ‘contraindications’ to ‘warnings’, and 30 mins monitor only for patients with PHT or unstable cardiopulmonary conditions, imposed post marketing safety studies

Oct 2011-12 – FDA removed monitoring requirements for PHT or unstable cardiopulmonary conditions, in packaging insert for Definity. Also remove statement that said efficacy and safety of these agents are not established in stress echo.

June 2014 – CHMP (division of EMA) removed ACS and unstable IHD as contraindications to Sonovue, but recommends 30 min monitoring

Oct 2016 – FDA rescinded shunt contraindications, added statement “when administering Optison to patients with a cardiac shunt, microspheres can bypass filtering of the lungs and enter the arterial circulation. Assess the patients with shunts for embolic phenomenon after Optison administration.”
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>UEA</th>
<th>Total patients</th>
<th>UEA patients</th>
<th>Control patients</th>
<th>Inpatient/outpatient</th>
<th>Rest/stress</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aggeli et al. (2008)</td>
<td>Prospective</td>
<td>Sonovue</td>
<td>5,250</td>
<td>5,250</td>
<td>NA</td>
<td>NR</td>
<td>Stress</td>
<td>No deaths or myocardial infarctions</td>
</tr>
<tr>
<td>Gabriel et al. (2008)</td>
<td>Retrospective</td>
<td>Definity or</td>
<td>9,798</td>
<td>4,786</td>
<td>5,012</td>
<td>95% Outpatients</td>
<td>Stress</td>
<td>No increased rate of SAEs or mortality at 24 h in UEA patients</td>
</tr>
<tr>
<td>Herzog et al. (2008)</td>
<td>Retrospective</td>
<td>Definity or</td>
<td>16,025</td>
<td>16,025</td>
<td>NA</td>
<td>Both</td>
<td>Both</td>
<td>No short-term mortality; SAEs in 0.031%</td>
</tr>
<tr>
<td>Kusnetzky et al. (2008)</td>
<td>Retrospective</td>
<td>Definity</td>
<td>18,671</td>
<td>6,196</td>
<td>12,475</td>
<td>Inpatients</td>
<td>Rest</td>
<td>No increased mortality in UEA patients</td>
</tr>
<tr>
<td>Main et al. (2008)</td>
<td>Retrospective</td>
<td>Definity</td>
<td>4,300,966</td>
<td>58,254</td>
<td>4,242,712</td>
<td>Inpatients</td>
<td>Rest</td>
<td>No increased mortality in UEA patients</td>
</tr>
<tr>
<td>Shaikh et al. (2008)</td>
<td>Retrospective</td>
<td>Definity or</td>
<td>5,069</td>
<td>2,914</td>
<td>2,155</td>
<td>Both</td>
<td>Stress</td>
<td>No increased risk for SAEs in UEA patients</td>
</tr>
<tr>
<td>Wel et al. (2008)</td>
<td>Retrospective</td>
<td>Definity or</td>
<td>78,383</td>
<td>78,383</td>
<td>NA</td>
<td>Both</td>
<td>Both</td>
<td>Severe allergic reactions in 0.01% and anaphylactoid reactions in 0.006%</td>
</tr>
<tr>
<td>Abdelmonaim et al. (2009)</td>
<td>Retrospective</td>
<td>Definity or</td>
<td>26,774</td>
<td>10,792</td>
<td>15,982</td>
<td>Both</td>
<td>Stress</td>
<td>No increased short- or long-term mortality in UEA patients</td>
</tr>
<tr>
<td>Anantharam et al. (2009)</td>
<td>Retrospective</td>
<td>Definity or</td>
<td>3,704</td>
<td>1,150</td>
<td>2,554</td>
<td>Both</td>
<td>Stress</td>
<td>No increased SAEs in UEA patients</td>
</tr>
<tr>
<td>Dolan et al. (2009)</td>
<td>Retrospective</td>
<td>Definity or</td>
<td>66,220</td>
<td>42,408</td>
<td>23,812</td>
<td>NR</td>
<td>Both</td>
<td>No increased mortality in UEA patients</td>
</tr>
<tr>
<td>Abdelmonaim et al. (2010)</td>
<td>Retrospective</td>
<td>Definity or</td>
<td>16,434</td>
<td>6,164</td>
<td>10,270</td>
<td>Both</td>
<td>Stress</td>
<td>No increased risk for myocardial infarction or mortality in UEA patients with pulmonary hypertension</td>
</tr>
<tr>
<td>Exuzides et al. (2010)</td>
<td>Retrospective</td>
<td>Optison</td>
<td>14,500</td>
<td>2,900</td>
<td>11,600</td>
<td>Inpatients</td>
<td>Rest</td>
<td>No increased mortality in UEA patients</td>
</tr>
<tr>
<td>Goldberg et al. (2012)</td>
<td>Retrospective</td>
<td>Definity</td>
<td>96,705</td>
<td>2,518</td>
<td>94,187</td>
<td>Both</td>
<td>Both</td>
<td>No increased mortality in UEA patients</td>
</tr>
<tr>
<td>Weiss et al. (2012)</td>
<td>Prospective</td>
<td>Definity</td>
<td>1,053</td>
<td>1,053</td>
<td>NA</td>
<td>NR</td>
<td>Both</td>
<td>No deaths or SAEs</td>
</tr>
<tr>
<td>Wever-Pincon et al. (2012)</td>
<td>Retrospective</td>
<td>Definity</td>
<td>1,513</td>
<td>1,513</td>
<td>NA</td>
<td>Both</td>
<td>Both</td>
<td>No deaths or SAE attributed to UEA in pulmonary hypertension patients</td>
</tr>
<tr>
<td>Platts et al. (2013)</td>
<td>Retrospective</td>
<td>Definity</td>
<td>5,956</td>
<td>5,956</td>
<td>NA</td>
<td>Both</td>
<td>Both</td>
<td>No increased mortality in UEA patients</td>
</tr>
<tr>
<td>Main et al. (2014)</td>
<td>Retrospective</td>
<td>Definity</td>
<td>32,434</td>
<td>16,217</td>
<td>16,217</td>
<td>Inpatients</td>
<td>Rest</td>
<td>Lower mortality in UEA patients</td>
</tr>
<tr>
<td>Wel et al. (2014)</td>
<td>Prospective</td>
<td>Optison</td>
<td>1,039</td>
<td>1,039</td>
<td>NA</td>
<td>Outpatients</td>
<td>Both</td>
<td>No deaths or SAEs</td>
</tr>
</tbody>
</table>

NA, Not applicable; NR, not reported; SAE, serious adverse event.
Modified with permission from Muskula et al. 26

Raised RVSP
Critically ill
Severe reactions that were considered “probably” related to an ultrasound contrast agent developed in 8 patients (0.01%), all of whom were outpatients, and 4 (0.006%) of these were consistent with anaphylactoid reactions.

- Variant of type I hypersensitivity reaction known as CARPA (Complement Activation Related Pseudo Allergy)
- No previous exposure necc, may not recur
- Higher rate in women, atopic individuals
- Range from mild wheezing to severe shock, hence, need crash cart with EpiPen standby
Current Status

- **Current Contraindications:**
  - *Definity* – known hypersensitivity to perflutren
  - *Optison* – known hypersensitivity to perflutren, blood, blood products, or albumin
  - *Lumason/Sonovue* – known hypersensitivity to sulfur hexafluoride or the inactive components of Lumason
  - Not for intra-arterial injections
  - Not advisable in pregnant women

- **Current BBW:**
  - Risk of serious cardiopulmonary reactions in patients with unstable cardiopulmonary conditions are rare and typically occurs within 30 mins

- Emerging safety data in LVAD and ECMO patients
LVO with Definity was performed in 40 patients at Day 3 – 5 acute anterior MI.

No major adverse events was seen. The only side effect observed was minor transient low back pain (9.4%), which resolved after 30 mins.

Since 2012, CGH has done 395 LVOs (Definity changed to Sonovue 2014)
- 59 (0.7%) SE, 336 (0.5%) resting TTE
- 1 anaphylactic shock (1 in 395, 0.25%) to Sonovue (Filipino lady with seafood allergy)
Conclusions

- EBD from LVO improves visualization of RWM and accuracy of stress echo
- VLMI is the preferred mode of imaging for LVO.
- Doppler enhancement is auxiliary when LVO is performed for imaging indications.
- UEA is safe to use, but requires vigilance for anaphylactoid reactions.
Thank you!