Updates on Ultrasound Contrast Agents

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Disclosures

- **Funding sources:**
  - NIH/CTSA Grant Number UL1 RR024150
  - Mayo Foundation
  - ASPER Foundation
  - Definity: Lantheus Medical Imaging Inc.
  - Optison: GE Healthcare Inc.
  - Vasodilator stress drugs (Adenosine and Regadenoson), Astellas Pharma Inc.

- **Off-label usage(s) of pharmaceuticals:**
  - Definity
  - Optison
  - SonoVue
Purpose

1. Recognize the clinical applications of Ultrasound Contrast Agents (UCA) “ASE updated guideline coming in 2018”

2. Brief look into the extended applications of UCA: myocardial perfusion, vascular, and cutting edge research

Outline

• Background
• LV Function Quantifications
• Cardiac Anatomy
• Intracardiac Masses
• Doppler enhancement
• Aortic Disease
• Regional LV Function (rest: ICU or ED, and Stress)

• Clinical impact and Cost Effectiveness
• Safety and Contraindications
• Pediatrics
• Extended Applications
• Summary
Sources


Agitated Saline Contrast

LV Functions Quantifications

Contrast Echo is Used

✓ To reduce variability and increase accuracy in LV volume and EF measured by 2D Echo
✓ To increase confidence of interpreting MD for LV function, structure and volume assessments

- LVEF
- HF devices
- Chemotherapeutics
- Valvular HD

2D Contrast Echo For LVEF/ Volumes

- 17 studies
- 2D Contrast Echo compared with other imaging modalities
- 2 multicenter studies including CMR
- Decreased intra-observer variability of EF measurements of contrast 2D echocardiography

LV Function In Heart Failure/Cancer Therapeutics

STICH trial(Core Lab) :

- LVEF ≤35% [enrollment criteria]
- LVEF measured by Core Lab >35% in 18.5% of patients!
- A reliable delineation of the LVEB was feasible from 2 apical views in 43.5% (recommended by ASE and EAE)
- Border detection from a single apical view only in 29.3%!

Oh JK et al. JASE. 2012; 25(3): 327–336

Cardiac Anatomy

Contrast Echo is Used

✓ To confirm or exclude the echocardiographic diagnosis of the LV structural abnormalities, when nonenhanced images are suboptimal for definitive diagnosis.
LV Apical Pseudoaneurysm


Cardiac Masses

**Contrast Echo is considered**

- When LV thrombi are suspected and not clearly documented or excluded on non contrast images
- Contrast perfusion may be used in patients with cardiac masses suspicious of a tumor to distinguish it from a thrombus when CMR is not available or inconclusive
LVAD and UCA

- 10 patients with LVAD underwent 12 TTE studies with contrast
- Contrast aided interpretation in 83%, contributed to a change in therapy in (5 pts) 42%
- No adverse events
- No change in device function parameters


UCA for Cardiac Masses (TEE)

| Presence of Thrombus, Artifacts, and Spontaneous Echo Contrast (SEC) According to Contrast Usage |
|-----------------------------------|-----------------|-----------------|-----------------|
| Contrast                        | Noncontrast     | P Value*        |
| Presence of SEC                 | 6/98 (6%)       | 32/98 (33%)     | <0.00           |
| Presence of artifact            | 2/98 (2%)       | 28/98 (29%)     | <0.00           |
| Presence of thrombus            | 6/98 (6%)       | 3/98 (3%)       | NS              |
| High level of confidence in excluding thrombus | 77/98 (79%) | 69/98 (70%) | 0.07 |

LA Myxoma

Differentiating Cardiac Masses using Contrast Echo Perfusion Imaging

- Malignancies have abnormal neovascularization
  Contrast hyperenhancement ➞ highly vascular or malignant tumor

  Stromal tumors (myxomas) ➞ a poor blood hypoenhanced

- Thrombi are generally avascular and show no enhancement

Abdelmonem SS et al, Echocardiography 2008;25:517

Kirkpatrick JN et al, JACC 2004; 43:1412-9
Contrast for Doppler Enhancement


Contrast Echo is Used
To Enhance Doppler Signals
✓ Aortic Stenosis
✓ Tricuspid Regurgitation for RVSP

Aortic Disease

• Detection of aortic dissection

• Location of non-visualized entry tear

• Contrast Echo is Used in Acute Aortic Syndromes:
  ✓ To assess aortic pathology if non contrast images and doppler are suboptimal

• In patients undergoing thoracic endovascular aortic repair procedures, contrast-enhanced TEE has improved endoleak detection [occurring in 10% to 45% of patients]

Regional LV Function

Contrast Echo is Used:
Rest, Stress, ED, ICU

- In difficult-to-image patients presenting with reduced image quality to
  - Obtain **diagnostic assessment of segmental wall motion** and thickening at rest and stress
  - Increase the proportion of diagnostic studies
  - Increase reader confidence in interpretation

Clinical utility of contrast was greatest in the lateral and anterior walls

- In these regions, the ability to distinguish normal from abnormal wall motion was increased from 78%→98% and 65%→88%, respectively

- Avoids foreshortening!

Hoffman R JASE 2014 27, 292-301
Contrast in Stress Echocardiography

Impact of contrast on visualizing segments and confidence of interpretation

- Patients referred for DSE: 1 with and 1 without a contrast agent [4 hrs apart]
- ↑ number of visualized /interpretable Segments
- ↑ diagnostic confidence

The OPTIMIZE Trial (n=101)

Impact of CEE on Patient Management

- N = 633 pt
- Uninterpretable studies ↓ from 11.7% to 0.3%
- Technically difficult studies ↓ from 86.7% to 9.8%
- Additional diagnostic procedures were avoided in 32.8%

“Cost-benefit analysis showed a significant savings using contrast of $122/patient.”

Kurt et al: JACC 53:802, 2009

Cost Effective Analysis stress CEE

- Premier, Inc. database query: Jan 2002 - Jun 2009
- 26,716 patients
- SE With and Without Definity® Contrast Agents
- Propensity-Matched Cohort
- Evaluating Length of Stay and Hospitalization Cost

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Regression coefficient</th>
<th>Transformed coefficient</th>
<th>p-value</th>
<th>Wald lower CI</th>
<th>Wald upper CI</th>
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<tbody>
<tr>
<td>LOS post-SE (days)</td>
<td>-0.033</td>
<td>0.967</td>
<td>0.002</td>
<td>0.948</td>
<td>0.987</td>
</tr>
<tr>
<td>Hospitalization Cost post-SE ($)</td>
<td>-0.051</td>
<td>0.951</td>
<td>&lt;.001</td>
<td>0.926</td>
<td>0.976</td>
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</tbody>
</table>

*Coefficients for LOS and cost were transformed to their original units of days for LOS and dollars for cost

- Controlling for clinical and demographic covariates, Contrast cohort had
  - 3.3% shorter LOS post-SE
  - 5.1% reduction in hospitalization cost

$216 in savings/patient

Abdelmoneim SS, Mulvagh SL; Canadian Cardiovascular Congress, Vancouver BC October 2014
### Safety of UCA

Life-threatening UCA reactions are rare (<1:10,000)

Parker JM, AJC 2013; 112; 1039–1045; Khawaja OA, AJC 2010; 106:742-747

![Figure 2. Pooled OR for all-cause mortality across studies between patients undergoing and not undergoing contrast imaging.](image)

### Contraindications to UCA

- Known or suspected right-to-left, bidirectional or transient right-to-left cardiac shunts
- Hypersensitivity to perflutren
- Intra-arterial injection
- 30-min monitoring:
  - Critically ill
  - Pulmonary hypertension (degree not specified)

Contrast Use in Peds

- Not associated with adverse effects used in patients without significant intracardiac shunts or severely increased PVR

- Can be helpful in patients in whom the benefit of enhanced EBD for cardiac structural assessment is clinically indicated

- Contraindicated in <5 years of age

- Not approved by the FDA


Extended Applications
Myocardial Perfusion

Off Label Use applied to clinical Practice:

1. Detection of perfusion abnormalities at rest (diagnosis of ACS)
2. Detection of Perfusion abnormalities during stress (incremental benefit over WM)
3. Detection of myocardial viability [IHD or stress induced cardiomyopathy]
4. Detection of microvascular no-reflow [ACS and microvascular functional abnormalities]
5. Detection of microvascular disease in Hyperglycaemic states/DM

Perfusion Echocardiography and TC cardiomyopathy

<table>
<thead>
<tr>
<th>Study, Year</th>
<th>Study Design</th>
<th>Number of Patients With TC</th>
<th>Number of Patients Evaluated With MCE</th>
<th>Results</th>
<th>Acute Stage</th>
<th>Follow-up</th>
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<tbody>
<tr>
<td>Ako et al, 2001</td>
<td>Case report</td>
<td>3</td>
<td>1 (qualitative)</td>
<td>Perfusion defect</td>
<td>Improved perfusion and WM</td>
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<td>Abe and Kondo, 2003</td>
<td>Case report</td>
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<td>Amaya et al, 2003</td>
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<td>Kasahara et al, 2005</td>
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<td>Upadhye et al, 2003</td>
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<td>Improved perfusion (2-3 months)</td>
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<td>Shah et al, 2006</td>
<td>Case report</td>
<td>1</td>
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<tr>
<td>Anzate et al, 2008</td>
<td>Case report</td>
<td>3</td>
<td>3 (qualitative)</td>
<td>Perfusion defect</td>
<td>Improved perfusion (2 wk) with MCE</td>
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<tr>
<td>Current study</td>
<td>Case report</td>
<td>9</td>
<td>1 (qualitative), 7 (quantitative)</td>
<td>Perfusion defect</td>
<td>Improved perfusion</td>
<td></td>
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</table>

Abdelmoneim et al. JASE 2009 30:45-55
Perfusion Echocardiography and STEMI (No Re-flow)

57 yo male, typical chest pain for 45 min
ECG: STEMI V1-4, elevated cardiac enzymes, PCI LAD
Perfusion Echo was done 3 hours post cath
(thrombectomy and stenting of mid LAD) with TIMI III flow

Abdelmoneim SS et al., Heart Vessels. 2015 Jan; 30(1):45-55

Diagnostic Accuracy of Stress Perfusion Echo for Detection of CAD (quantitative analysis)

- 13 studies
- 627 patients
- quantitative analysis in 574 (92%) patients

**Contrast Perfusion Echocardiography Stress Protocols**

- **Dobutamine (μg/kg/min)**
  - 0
  - 10
  - 20
  - 30
  - 40

- **Recording:**
  - LV wall motion + Perfusion

- **Atropine (0.3 mg, maximum 1.2 mg) is given, if there is no adequate increase in heart rate.**

**Re gadolinium RTMCE Protocol**

- **Rest**
- **Stress Echo:**
  - AECG, AECA, A20

**Coronary Vascular Imaging and Flow**

- **718 patients**
- **Evaluated for known or suspected CAD**
- **Followed up for 16 months**

“The multiparametric assessment of WM, CFR-LAD, and MP during stress testing is feasible, identifies patients at increased risk for cardiac events more accurately than usual standard WM assessment, and separates them from those with normal findings who are at much lower risk,....”

Diagnostic Accuracy of Contrast Stress Perfusion Echo for Detection of CAD

### Vasodilators Stress

<table>
<thead>
<tr>
<th>Patients (n)</th>
<th>Stress method (vasodilator)</th>
<th>Patients undergoing coronary angiography</th>
<th>CAD present</th>
<th>Sensitivity</th>
<th>Specificity</th>
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<th>Year</th>
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<td>Galassi et al. 2010</td>
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<td>77</td>
<td>73</td>
<td>Abdollehnoos et al. 2015</td>
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Mean (95% CI): 35.71 (37.56 - 33.80)

Senior R et al, EHJ- CV Imaging, 2017:18,1205

### Dobutamine or Exercise Stress

<table>
<thead>
<tr>
<th>Patients (n)</th>
<th>Stress method (dobutamine or exercise)</th>
<th>Patients undergoing coronary angiography</th>
<th>CAD present</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Author</th>
<th>Year</th>
</tr>
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<tr>
<td>45</td>
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<td>66</td>
<td>Cowig et al. 2000</td>
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<tr>
<td>100</td>
<td>Exercise (treadmill or bike)</td>
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<td>75</td>
<td>100</td>
<td>Simon et al. 2001</td>
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<td>93 (qualitative)</td>
<td>80 (qualitative)</td>
<td>Moczkaj-jenke et al. 2013</td>
<td></td>
</tr>
</tbody>
</table>

3852 (total) | 1070 (total) | 795 | Mean(95% CI): 88 (94-91) | Mean(95% CI): 77 (69-85) |

Senior R et al, EHJ- CV Imaging, 2017:18,1205
Prognostic Role of Contrast Stress Perfusion Echocardiography for detection of All cardiovascular event and Hard Event (death and non fatal MI)

Senior R et al, EHJ- CV Imaging, 2017:18,1205

Tsutsui JM et al: Circulation 112:1448, 2005
UCA Emerging Clinical Applications

• Early detection of chemotherapy induced cardiotoxicity
• Insulin Resistance
• Novel T2D Therapy: GLP-1 therapy
• Carotid CEUS
• Detection of rejection Cardiac allograft vasculopathy (CAV) in heart transplant patients

Carotid CEUS

Relationship of Intraplaque Neovascularization, Cardiovascular events: A microbubble Contrast Enhancement Ultrasound study: Interim Results

Quantifications of Intraventricular Vortices

- Ultrasound agents have been used for quantitative analysis of intraventricular flow dynamics [kinetic energy] and assessment of LV vortex
- Serial monitoring of energy dissipation changes over time
- New parameter on LV pump efficiency (heart failure application)

Agati et al., EHJ- Cardiovascular Imaging, 15, 11, 2014, 1203–1212

Cutting Edge Basic Research

- Evaluate Tumor response to new antiangiogenic therapy
- Therapeutic applications Sonothrombolysis and Gene/drug delivery
- Molecular Imaging of Inflammation

Kisling et al. J Nuc Medicine 2012; 53:345
SUMMARY

1. UCA is essential to clinical echocardiography practice when Echo images are suboptimal: to (serially) quantitate, and to exclude/differentiate certain diagnoses—Quality assurance

2. Microbubbles and ultrasound interact— operator skill-- Learning curve

3. Cost but there is benefit

4. UCA are safe, have no radiation [0 mSv]

5. Contrast perfusion Echo complement wall motion analysis— incremental information [yet remains off-label] bedside rapid detection for ischemia

6. Quantification can be performed to obtain MBF (dB/sec or ml/min/g), although; qualitative adequate

Thank You!