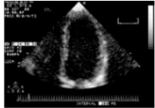


# CLINICAL APPLICATIONS OF CONTRAST ECHO: ASE 2018

Adj Assoc Prof. Tong Khim Leng  
MBBS MRCP FAMS FACC FASE FRCP  
Chief, and Sn Consultant  
Echo Director

Department of Cardiology, Changi General Hospital  
Singapore



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## Disclosure

- Monthly Echo conference lunch by Sonovue distributor



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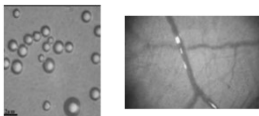
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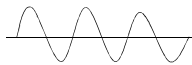
## 2 Components of CE (Contrast Echo)

UCA → UEA

(ultrasound contrast → enhancing agents)



Ultrasound waves  
(System Technologies)



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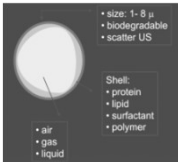
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## Approved 2<sup>nd</sup> Generation Microbubbles

Name	Manufacturer/Vial contents	Mean diameter	Shell	Gas	Contraindications
Lumason (sulfur hexafluoride lipid-type A microspheres)	Bracco Diagnostics, 5 mL	1.5-2.5 $\mu$ m (maximum 20 $\mu$ m, 99% < 10 $\mu$ m)	Phospholipid	Sulfur Hexafluoride	Allergy to sulfur hexafluoride
Definity (perflutren lipid microspheres)	Lantheus Medical Imaging, 1.5 mL	1.1-3.3 $\mu$ m (maximum 20 $\mu$ m, 98% < 10 $\mu$ m)	Phospholipid	Perflutren	Allergy to perflutren
Optison (perflutren protein type-A microspheres)	GE Healthcare, 3.0 mL	3.0-4.5 $\mu$ m (maximum 32 $\mu$ m, 95% < 10 $\mu$ m)	Human albumin	Perflutren	Allergy to perflutren/ blood products



FDA approved – Lumason (Sonovue), Definity and Optison

Europe EMA approved – Sonovue

Singapore HSA approved – Definity, Sonovue




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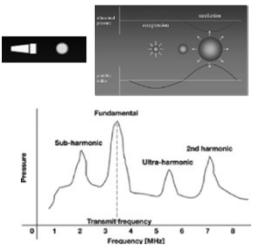
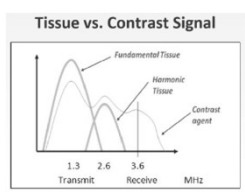
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**Bubbles oscillate non linearly, whilst myocardium oscillate linearly.**

CE aim to enhance non linear signals from bubbles while suppressing linear signals (noise) from myocardium, i.e. increase signal to noise ratio, by using special imaging mode.

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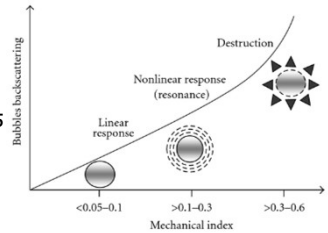
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### Mechanical Index (MI)

**Very Low MI (VLMi) < 0.2**  
**Low MI < 0.3**  
**Intermediate MI = 0.3 – 0.5**  
**High MI > 0.5**



MI =  $\frac{PNAP}{\sqrt{\text{freq}}}$

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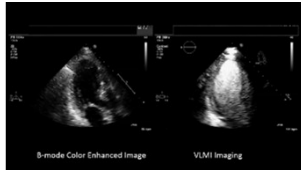
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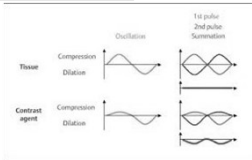
**CE imaging mode rec by ASE 2018:  
B mode low MI harmonic vs Very Low MI (VLMI)**



Brief 5-10 frames of high MI flash can be used to clear contrast from myocardium

**VLMI (very low MI < 0.2) imaging recommended by ASE 2018**

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



VLMI : multipulse tissue cancellation techniques

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**ASE 2018:  
Clinical Applications of UEAs  
(Adult Cardiac Applications)**

1. Left Ventricular Opacification (LVO)
  - only FDA approved use
2. Myocardial Perfusion Echocardiography (MCE)
  - Off label , still recommended by ASE 2018
3. Sonoporation - Targeted drug and gene delivery
  - Research




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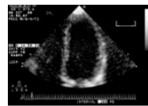
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**Indications for LVO**



1. **For accurate assessment and/or quantification of RWM, LVEF and LV volumes**
  - 5 -15% of patients and upto 30% of ICU patients due to obesity, lung diseases, mechanical ventilation or chest deformities.
2. **To confirm or exclude LV structural abnormalities**
  - LV non-compaction, apical LV clot, HCM, cardiac mass, complications of myocardial infarction eg LV pseudoaneurysm, aneurysm, myocardial rupture.
3. **Enhancement of Doppler signals eg TR, AS.**
  - usually when UEA is used for other imaging indications




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**1. Updates on Quantification of LV volumes, LVEF, and RWM**

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 use of UEs should be used when two or more LV segments which the study indication requires the assessment of LV function (LVEF and RWM) and/or study indication requires accurate analysis of RWM (COR 1, LOE A)
- 2. A brief (5- to 10-frame) high-MI (0.8-1.2) imaging to clear myocardium of contrast and for volume and ejection fraction measurements
- 3. Ultrasound enhancement should be used in assessment of LVEF is important to prognosis or VLMi and low-MI harmonic imaging techniques (COR 1, LOE A)
- 4. LV volumes obtained by enhanced echocardiography measured without UEs, and therefore 2018 ASE should be applied with caution when data are normal range for LVEF does not appear to end-diastolic and end-systolic LV volumes
- 5. As per section (i) of the 2018 ASE guidelines, a low-volume (<0.5 mL) bolus injection is recommended along with VLMi imaging technique and basal segment attenuation.
- 3. Ultrasound enhancement should be used in ALL patients in whom quantitative assessment of LVEF is important to prognosis or management of the clinical condition - kivi ICD/CRT imaging technique - cardiotoxicity from chemotherapy - valve disease for intervention

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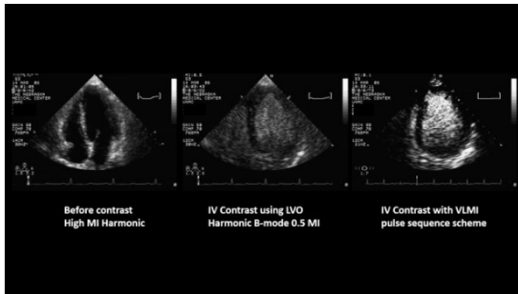
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VLMI imaging improves apical and basal segments visualisation

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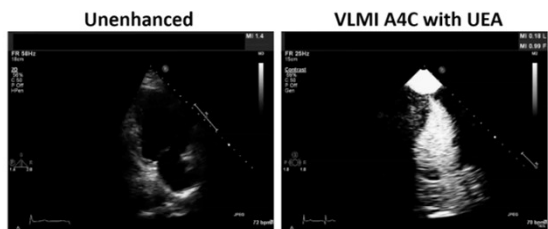
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VLMI improved assessment of RWMA

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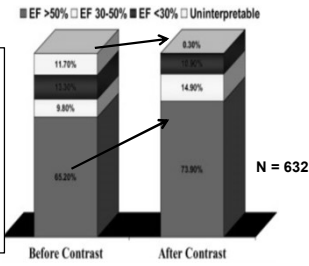
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**Contrast improves interpretation of resting wall motion, LVEF and measurement of LV volumes**

- 11% reduction in uninterpretable studies
- LVEF appeared better with contrast
- CE leads to change in mx in 35.5% of patients, particularly in sickest patients in SICU



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

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**2. Key Points and Recommendations for the Use of UEAs in Detecting LV Cavity Abnormalities and Intracardiac Masses**

1. Ultrasound enhancement should be used in patients in whom LV thrombus cannot be ruled in or out with noncontrast echocardiography (COR I, LOE B-NR).
2. Ultrasound enhancement should be considered in patients in whom structural abnormalities of the LV and aortic valve are suspected. ... US enhancement should be used for LV thrombus, structural abnormalities eg noncompaction, apical HCM, LV pseudoaneurysm, assess vascularity of mass with VLMI.
3. Ultrasound enhancement should be used in patients in whom LV thrombus cannot be ruled in or out with noncontrast echocardiography (COR I, LOE B-NR).
4. Ultrasound enhancement should be used in patients in whom structural abnormalities of the LV and aortic valve are suspected.
5. Ultrasound enhancement should be considered during TEE whenever the atrial appendage has significant spontaneous contrast or cannot be adequately visualized with unenhanced imaging (COR IIa, LOE B-NR)

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**60 yr Obese DM gentleman admitted for heart failure**



Unenhanced echo      B mode 2<sup>nd</sup> harmonic low MI imaging

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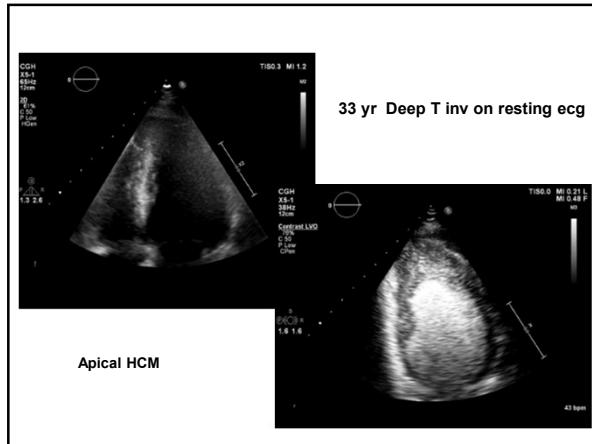
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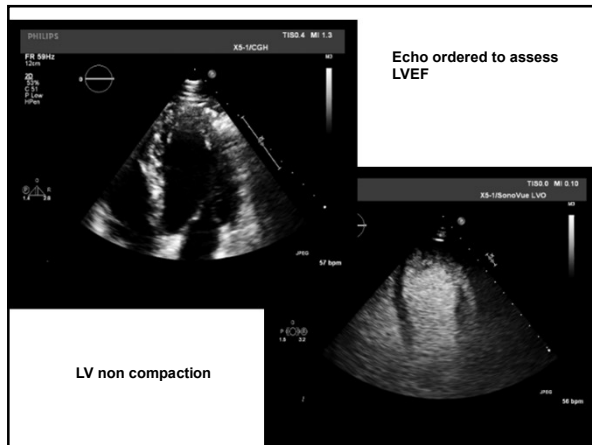
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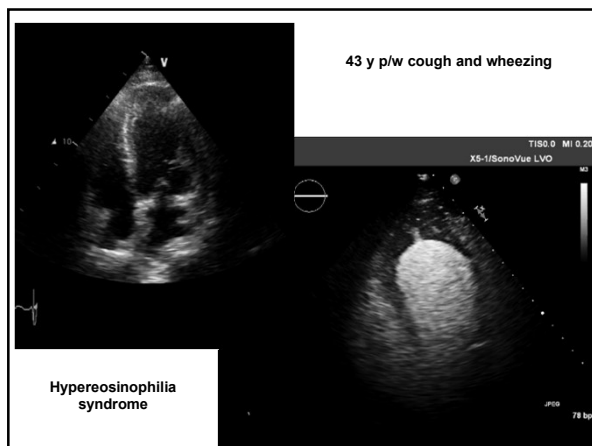
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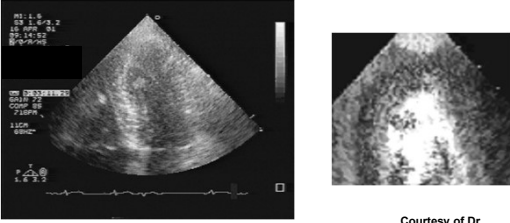
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**56 yr old Caucasian with h/o melanoma**  
**Benign Vascular mass: LV Cavernous Haemangioma**



Courtesy of Dr. Lepper

**Differentials of LV mass**

**Malignant** : metastatic melanoma, sarcomas (angiosarcoma)  
 - Typically more vascular

**Benign** : myxoma, lipoma, fibroma, papillary fibroelastoma, haemangioma

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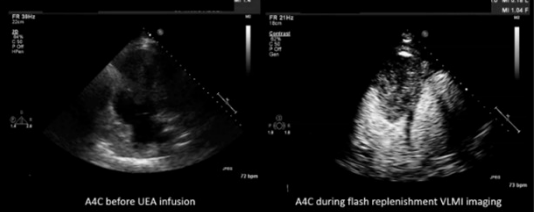
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**Malignant Vascular mass: Renal Cell Carcinoma**

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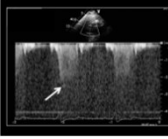
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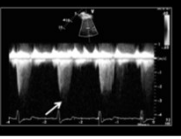
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**3. Contrast enhancement of Doppler signals**  
 (ASE 2018: COR 1, LOE C-E0)

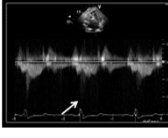
- When UEAs being used for imaging..
- To enhance TR jet (for RVSP), and peak velocity in valvular stenosis
- Important to reduce Doppler gain to minimize noise and blooming artefact



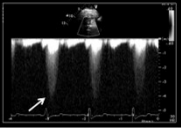
TR w/o contrast  
Vmax = 2.5 m/s



TR with contrast:  
Vmax = 3.0 m/s



AS w/o contrast  
PPG = 30 mmHg



AS with contrast  
PPG = 70 mmHg

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## Myocardial contrast echo (MCE): The Holy Grail of CE

Recommendations 4 to 7 pertain to those individuals who have received recommended training in perfusion imaging techniques with UEAs

4. Although perfusion imaging with UEAs is off label, ischemia and viability can be enhanced when used.
5. If performing MPI imaging, VLM perfusion imaging stress using mid-dose high-MI flash replenishment, in-stress and wall motion assessment (COR IIa, LOE B-R).
6. Perfusion analysis combined with BWM analysis using short DSE to maximize the sensitivity and accuracy of CAD and prediction of clinical outcome (COR IIa, LOE B-R).
7. Standard (0.56 mg/kg) or high-dose (0.84 mg/kg) of EFMCE should stress both MPI and BWM to maximize of CAD (COR IIa, LOE B-R).
8. Adrenergic and vasodilator stress should be performed with MPI to maximize the sensitivity and specificity of MPI and BWM to maximize the sensitivity and accuracy of CAD (COR IIa, LOE B-R).
9. When homogeneous myocardial contrast is observed weekly, repetitive bolus doses of 0.56 mg/kg of high-MI flash and adjusted to clear myocardial contrast signals before the detection of the high-MI bolus should be used for frames should be adjusted to clear myocardial contrast.
10. The replenishment for a 2D imaging plane should be in resting conditions and within 2 sec to a constant intensity imaging. Figure 11 demonstrates normal recovery following high-MI impulses. Figures 12 and 13 depict in different coronary artery territories during MCE. Quantitative MCE appear to have additional value of myocardial blood flow abnormalities due to significant software capable of analyzing myocardial regional following high-MI impulses. It is not uncommon and readily available software is available on the market. The Working Group recommends that all vendors do their systems for analyzing replenishment rates and high-MI impulses within any chosen region of interest.

Although perfusion imaging is off label, detection of myocardial ischaemia and viability can be enhanced when used in the correct setting by trained personnel...

..VLMi with real time high MI flash replenishment technique.. Simultaneous perfusion and wall motion assessment to maximise sensitivity of CAD detection. (COR IIa, LOE B-R)

.. During DSE or vasodilator stress (COR IIa, LOE B-NR)  
.. Either infusion or repetitive bolus of UEA..

.. Replenishment of flow should be within 5 sec at rest and within 2 sec during stress following high MI flash..

... Quantitative MCE, requires dedicated software.. Not rec for clinical application yet until vendors develop software..

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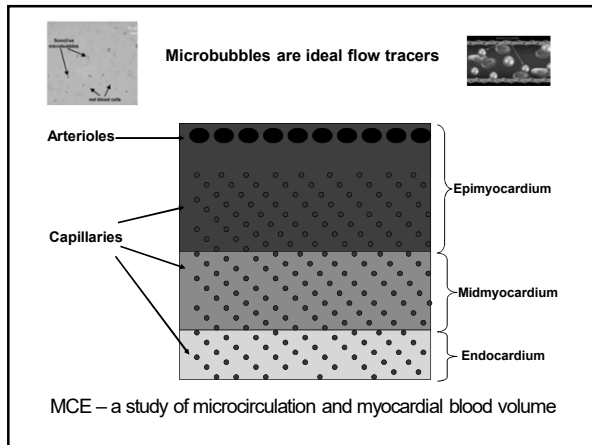
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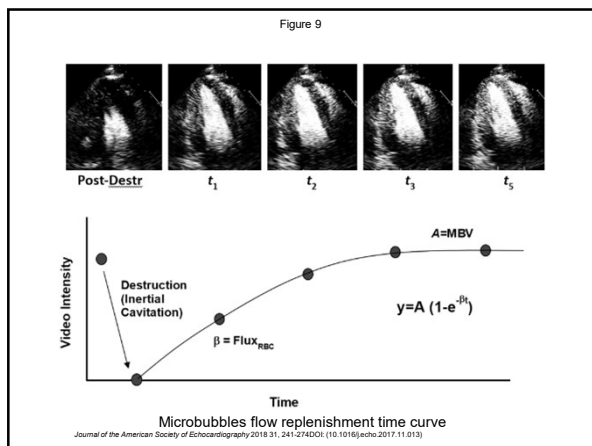
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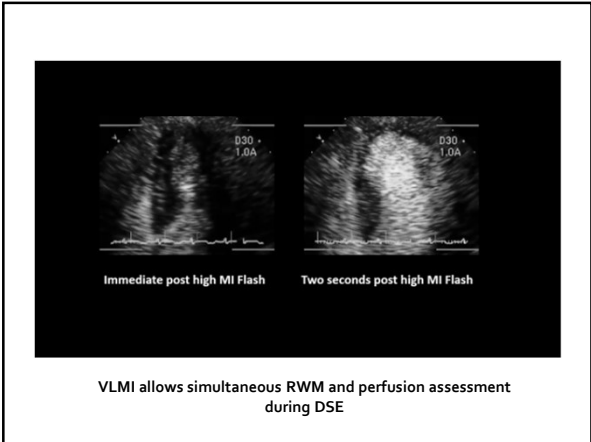
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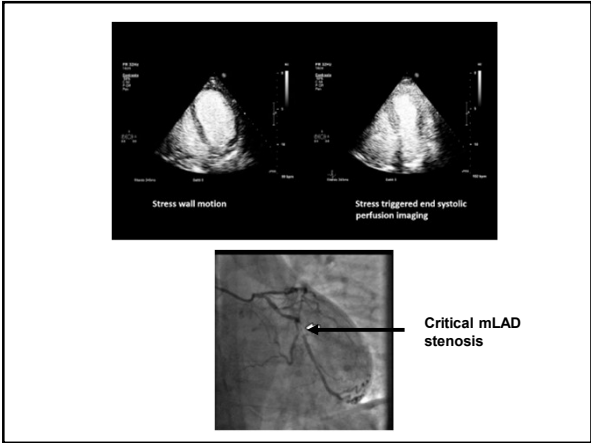
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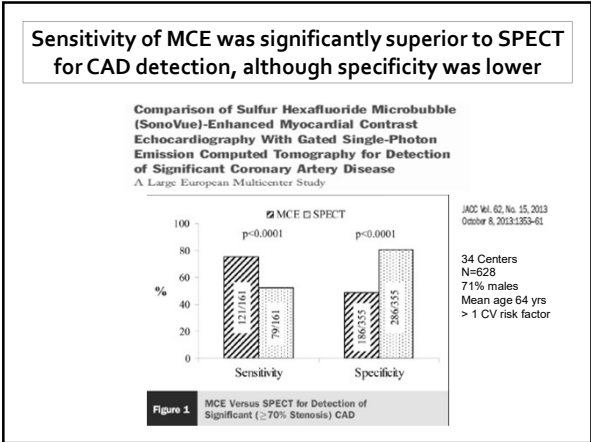
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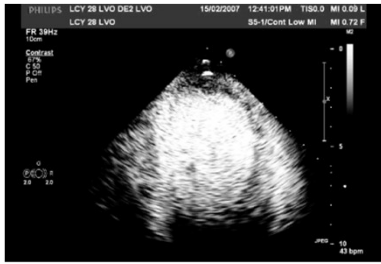
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**MCE is able to assess the transmuralty of myocardial infarction**



Anterior STEMI  
 -TIMI 3 flow in epicardial LAD  
 -transmural defect in apical cap, subendocardial  
 perfusion defect in apical lateral wall




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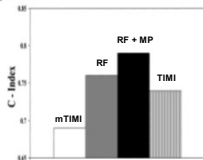
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**RF and MP from CE provides incremental prognostic value in patients presenting to ED with chest pain**

**EXPANDED REVIEW**  
 Myocardial Contrast Echocardiography Versus Thrombolysis in Myocardial Infarction Score in Patients Presenting to the Emergency Department With Chest Pain and a Nondiagnostic Electrocardiogram  
 Xiao-Ling Tang, MD,†; Jiahui Tang, MD, FACC;†; Xia-Qin Wang, MD,†; Dong-Huokoh, MD, FACC;†; Suni Kwon, MD,†; Jiahui Bickel, MD, FACC;†; Xun-Qin Wang, MD,†; Dong-Huokoh, MD, FACC;†; Kevin Wu, MD, FACC;†  
 †Chonnam National University Medical Center, Gwangju, Korea



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.

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**Contrast is SAFE**

- Since black box by FDA in 2007, innumerable studies in rest and stress echo, critically ill patients, pulmonary hypertension demonstrated safety.
- Contraindication of right to left shunt removed in 2017
- Emerging safety data in LVAD and ECMO patients
- **Current Contraindications:**
  - known hypersensitivity to products
  - 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

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**The Safety of Definity and Optison for Ultrasound Image Enhancement: A Retrospective Analysis of 78,383 Administered Contrast Doses**

Kevin Wei, MD, Sharm S. Maheshwari, MD, Lisa Carson, MS, Boris Dandoff, MD, Rustin Cabell, MR, CSR, Richard A. Grimm, DO, Stephanie Wilson, MD, Lorenz Fain, MD, Charles A. Herring, MD, William A. Ziegler, MD, FASE, Elizabeth Taylor, MS, DRCR, Michael Forster, MD, Parag S. Chaudhry, MD, Thomas R. Porter, MD, Walid Issa, MD, FASE, and Roberto M. Lang, MD, FASE, Portland, Oregon; Rochester, Minnesota; Memphis, Tennessee; Boston, Massachusetts; Cleveland, Ohio; Atlanta, Georgia; Birmingham, Alabama; Houston, Texas; Kansas City, Missouri; New York City, New York; Omaha, Nebraska; Nashville, Tennessee; and Chicago, Illinois



Severe reactions .....developed in 8 patients (0.01%), all of whom were outpatients

4 (0.006%) of these were consistent with anaphylactoid reactions.

Background: The mean age of patients who received an intravenous contrast agent was 60 years, 66% were male, and the mean body mass index was 32 = 1.4 g/cm<sup>2</sup>.

Method: All patients who received a contrast agent during the study period were included in the analysis.

Results: 78,383 contrast doses were administered to 40,000 patients. There were 8 severe reactions (0.01%) and 4 anaphylactoid reactions (0.006%).

Conclusion: Severe reactions to contrast agents are rare. Anaphylactoid reactions are a variant of type I hypersensitivity reaction known as CARPA (Complement Activation Related Pseudo Allergy). Range from mild wheezing to severe shock, hence, need crash cart with EpiPen standby.

Keywords: Adverse events, Contrast agent, Echocardiography, Safety, Ultrasound

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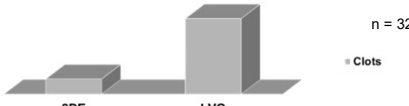
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**Diagnostic Utility of Contrast Echocardiography For Detection of Left Ventricular Clot in An Asian Population with Acute Anterior ST Elevation Myocardial Infarction**

Chai SC, Tong K L et al CGH, SCC and Euroecho 2007



LVO done in Day 3 – 5 acute anterior MI. 40 Singaporean Asian patients.

No major adverse events was seen with Definity. The only side effect was minor transient low back pain (9.4%).

Since 2012, CGH has done >400 LVOs (Definity, Sonovue)

- no back pain
- 1 anaphylactic shock (0.2%) to Sonovue

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## Conclusions

- LVO at rest (2 or more segments not visualized) and stress echo (any segment not visualized) remains the only approved indication for UEA by FDA.
- Growing data show myocardial perfusion study with UEA is feasible clinically and adds incremental value to wall motion.
- UEA is safe to use. SAE is about 1 in 10000. Users should be watchful for possible anaphylactoid reactions.




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*Thank you!*



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