12th Annual Multimodality Cardiovascular Imaging for the Clinician

# Contrast Echocardiography:
# *Powerful Tool*
# *in Diagnosis and Management*

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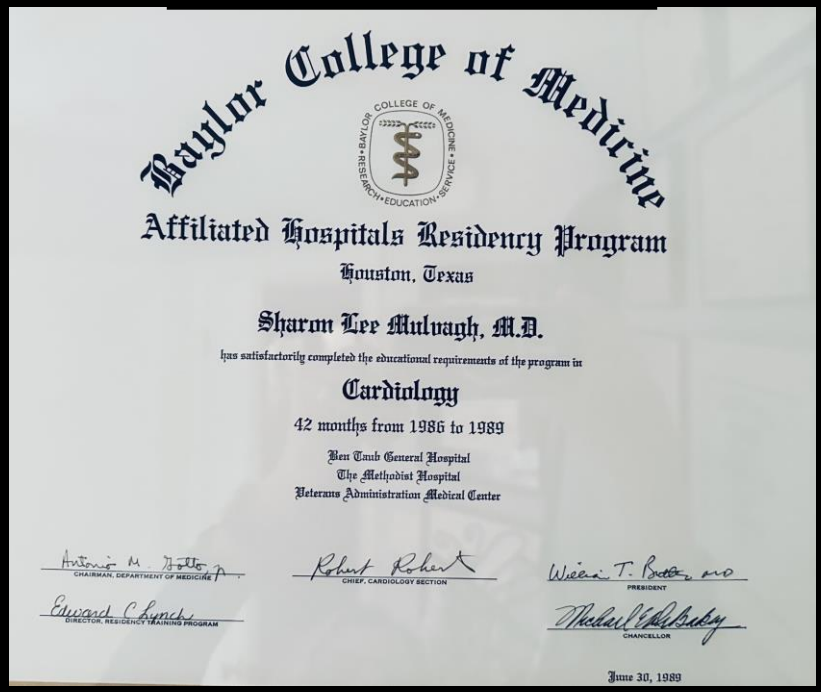
# Disclosures:

Novo Nordisk:

Consultant; honoraria

Lantheus Medical Imaging:

Consultant; honoraria



Baylor College of Medicine

COLLEGE OF MEDICINE • BAYLOR • RESEARCH • EDUCATION • SERVICE

Affiliated Hospitals Residency Program

Houston, Texas

Sharon Lee Mulvagh, M.D.

has satisfactorily completed the educational requirements of the program in

Cardiology

42 months from 1986 to 1989

Ben Taub General Hospital
The Methodist Hospital
Veterans Administration Medical Center

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June 30, 1989

# Please  if your Echo Lab

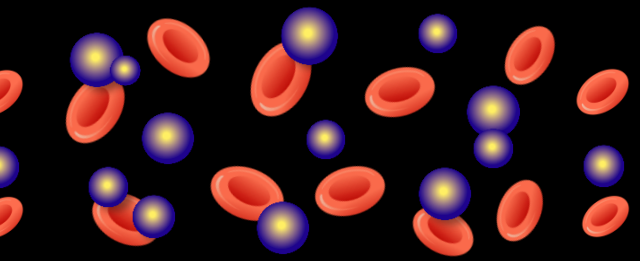
- Uses contrast daily?
- Has a policy enabling sonographers to:
  - Make a decision to give contrast?
- Has a policy enabling sonographers to:
  - Start IV's
- Uses contrast for perfusion imaging?

# Objectives

- Recognize clinical situations in which contrast echo can establish a diagnosis and guide management through case-based examples
- Discuss how to optimize images
- Develop a strategy for use in your echolab

# What is Contrast Echo?

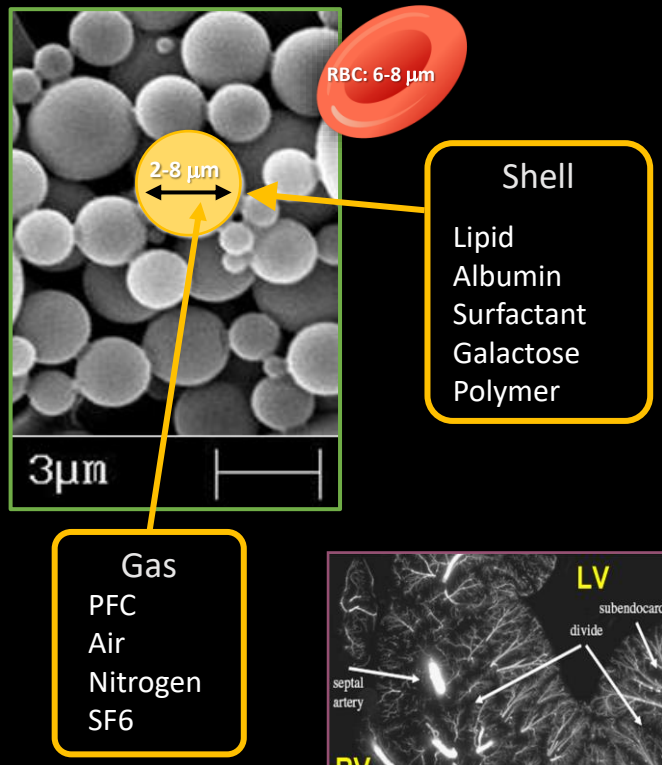
- **Well-studied, safe imaging technique**
- **Ultrasound Enhancing Agents (UEA)**
  - **microbubbles = "contrast echo"**

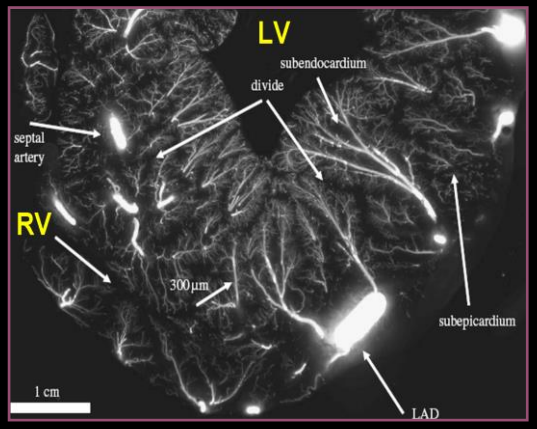



- **Optimize evaluation of LV function (LVO/EBD)**
- ***Simultaneous* assessment of perfusion ("off-label")**

Burns et al: Diagnostic Ultrasound1:57, 1998

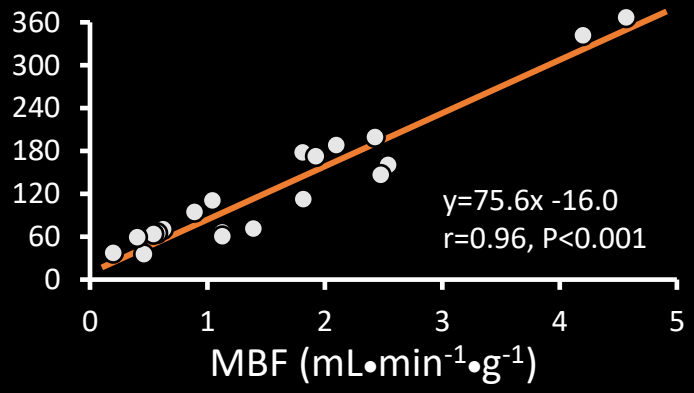
# Ultrasound Enhancing (Contrast) Agents




Spaan et al. Phil. Trans. R. Soc. A , 2008

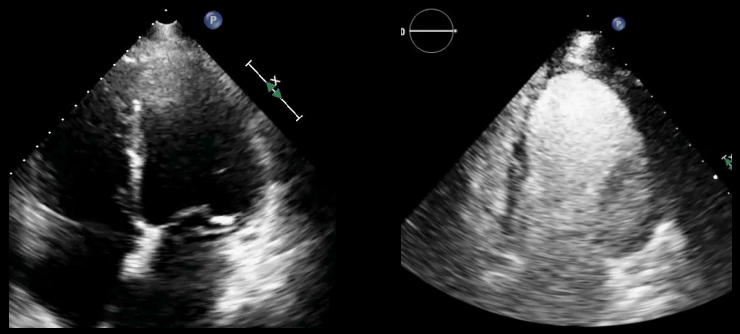
- Nontoxic/inert
- Small to pass pulmonary vasculature
- Persistent enough to reach the LV and/or myocardium
- **Pure intravascular tracers**




Burns et al: Diagnostic Ultrasound, 1998
Wei et al: Circulation, 1998

# Approved* UEA's

*FDA-USA, ^Health Canada

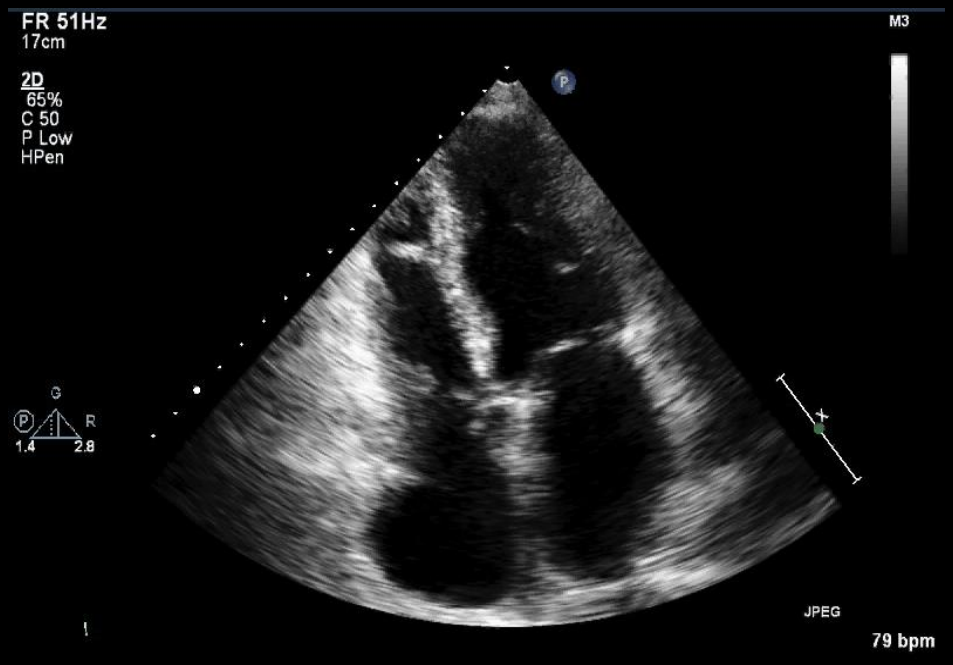


| UEA | SIZE (μm) | Gas | Shell | Indication |
|---|---|---|---|---|
| ^*Optison™ | 3.0-4.5 | Perflutren | Albumin | LVO/EBD |
| ^*Definity® | 1.3-3.3 | Perflutren | Phospholipid | LVO/EBD |
| ^Sonovue *Lumason™ | 1.5-2.5 | SF6 | Phospholipid | LVO/EBD |

- Approved use: left ventricular opacification (LVO) and endocardial border delineation (EBD)
- Off-label use for myocardial perfusion

*Porter TR, Mulvagh SL et al. J Am Soc Echocardiogr 2018 31, 241-274*

# 67 yo female s/p heart transplant



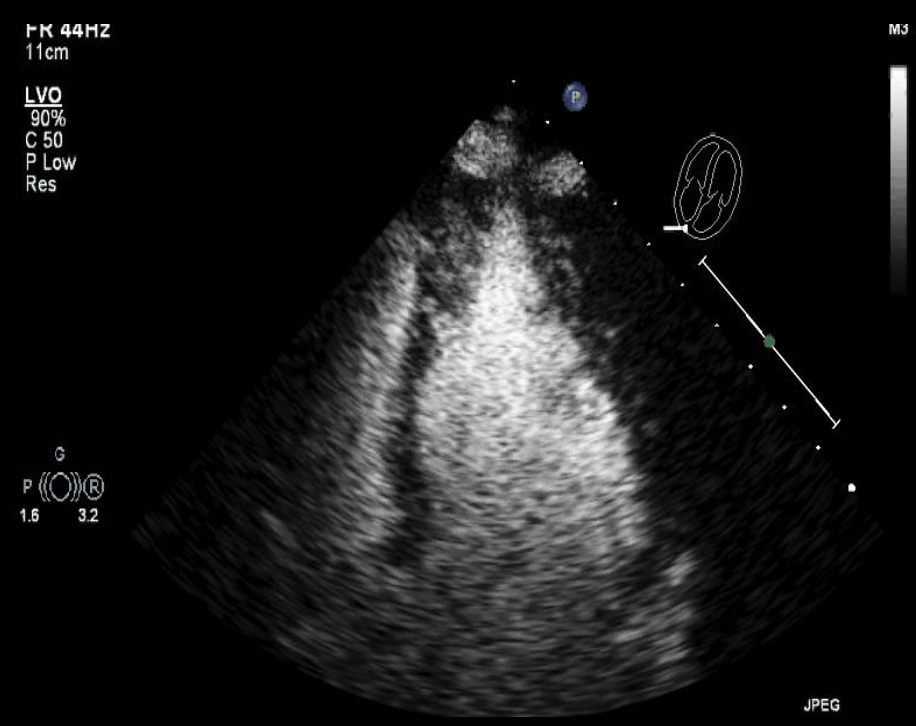

4-C


2-C

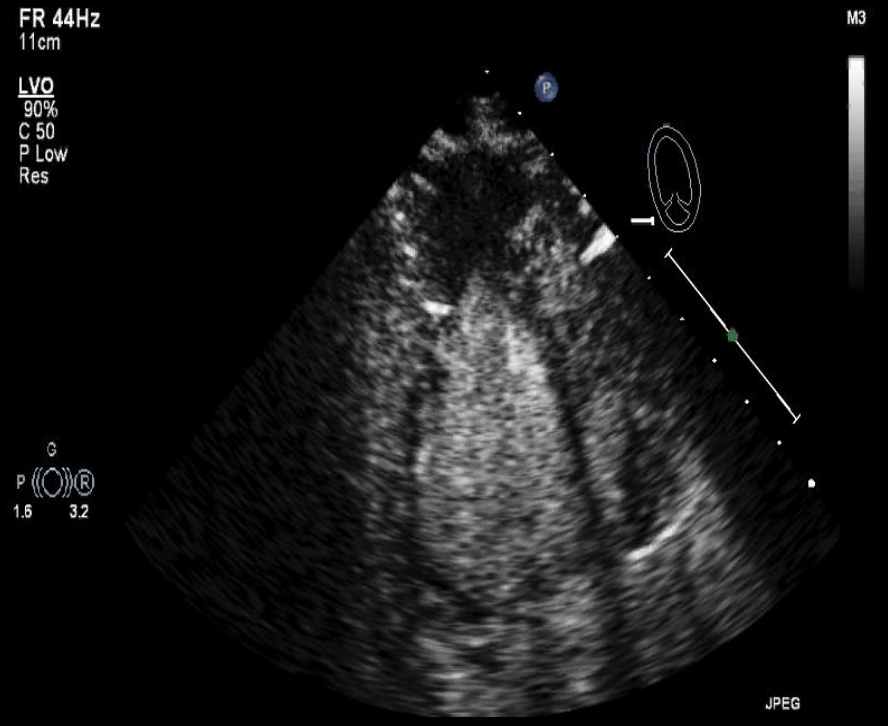
The findings seen  are most consistent with:

1. Coronary artery disease
2. Sarcoidosis
3. Myocarditis
4. Hypereosinophilic syndrome
5. Hypertrophic cardiomyopathy

# *Contrast Images:*




4-C



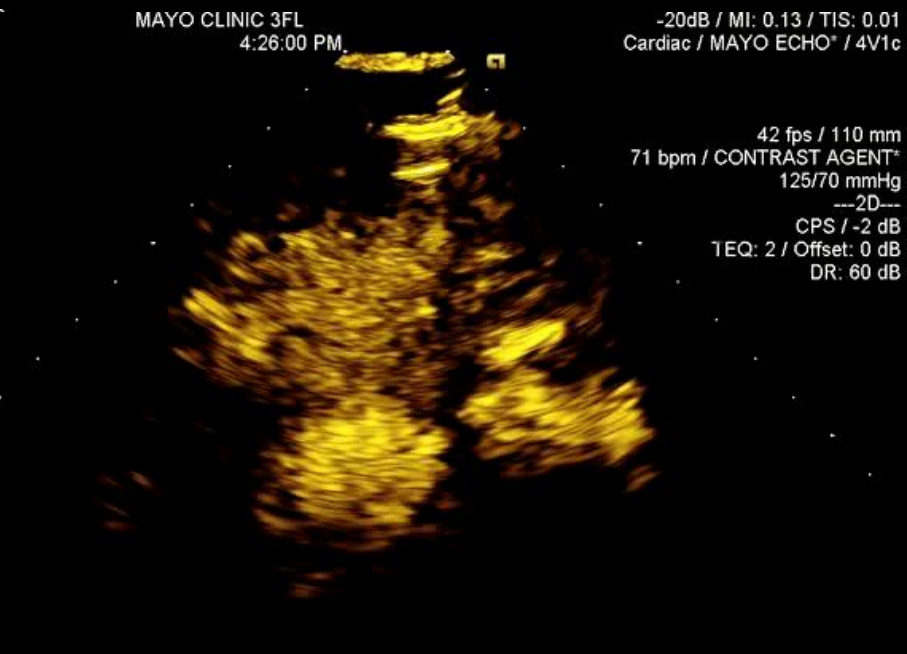

2-C

**No apical RWMA**

**Diagnosis: Apical Hypertrophic Cardiomyopathy**

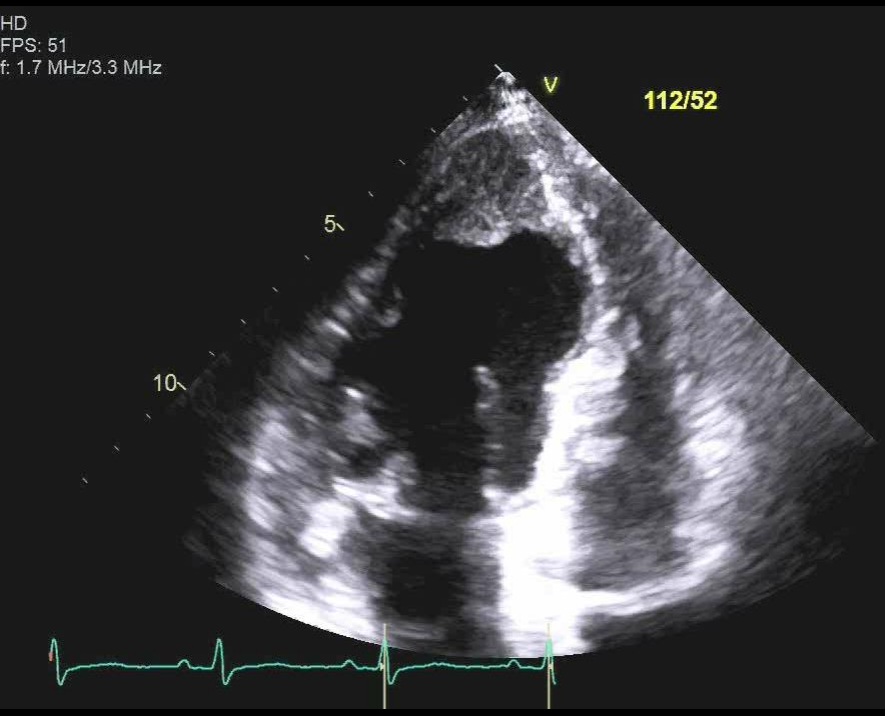
# Contrast – Helpful to diagnose LV Apical Abnormalities


HCM - Apical Aneurysm – Thrombus?

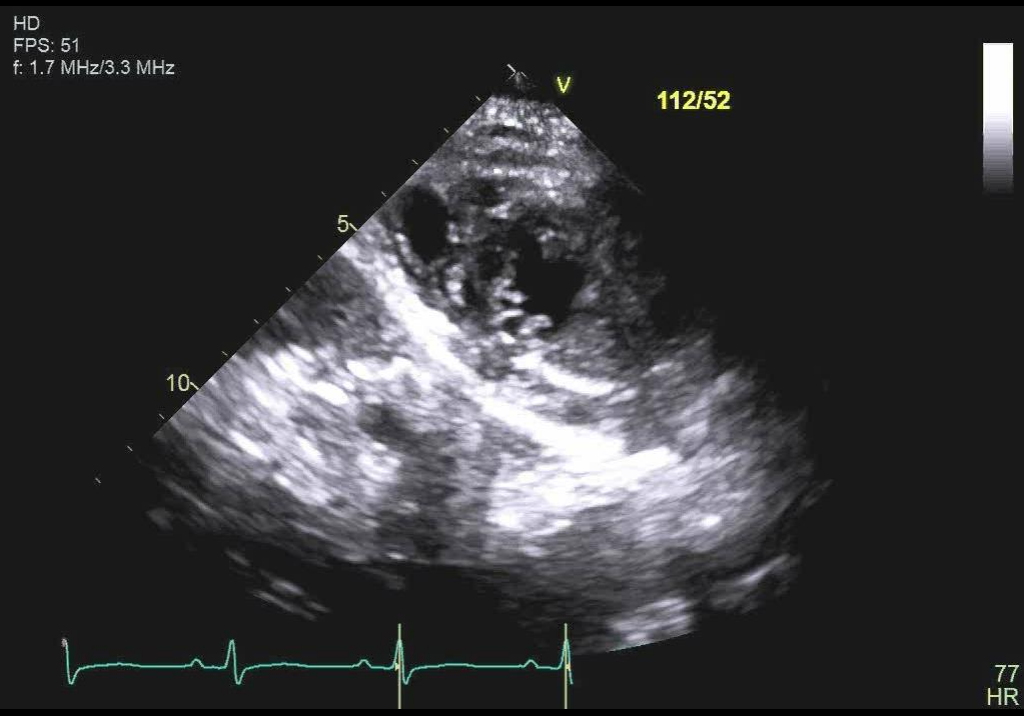



No thrombus

# 34 yo female with headache, chest and jaw pain

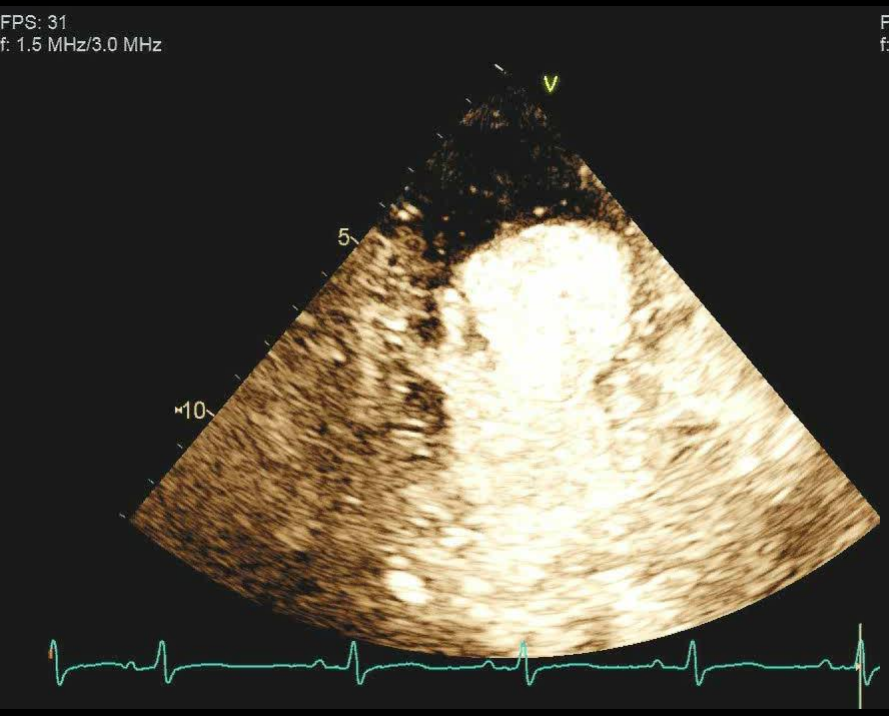



4-C

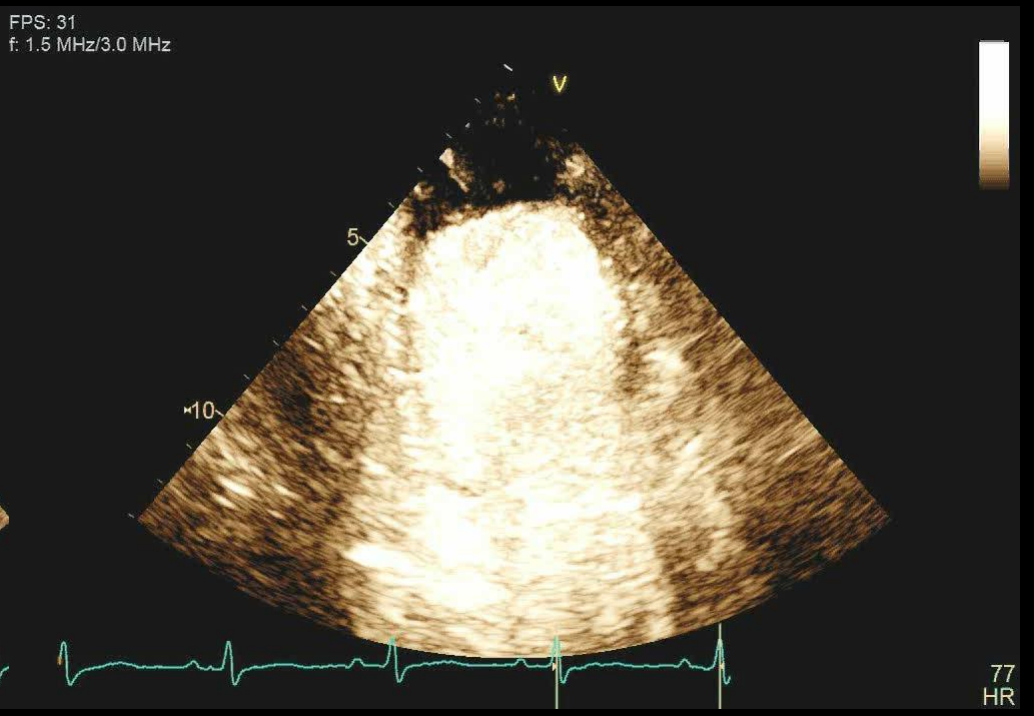



Apical SAX

# *Contrast Images:*

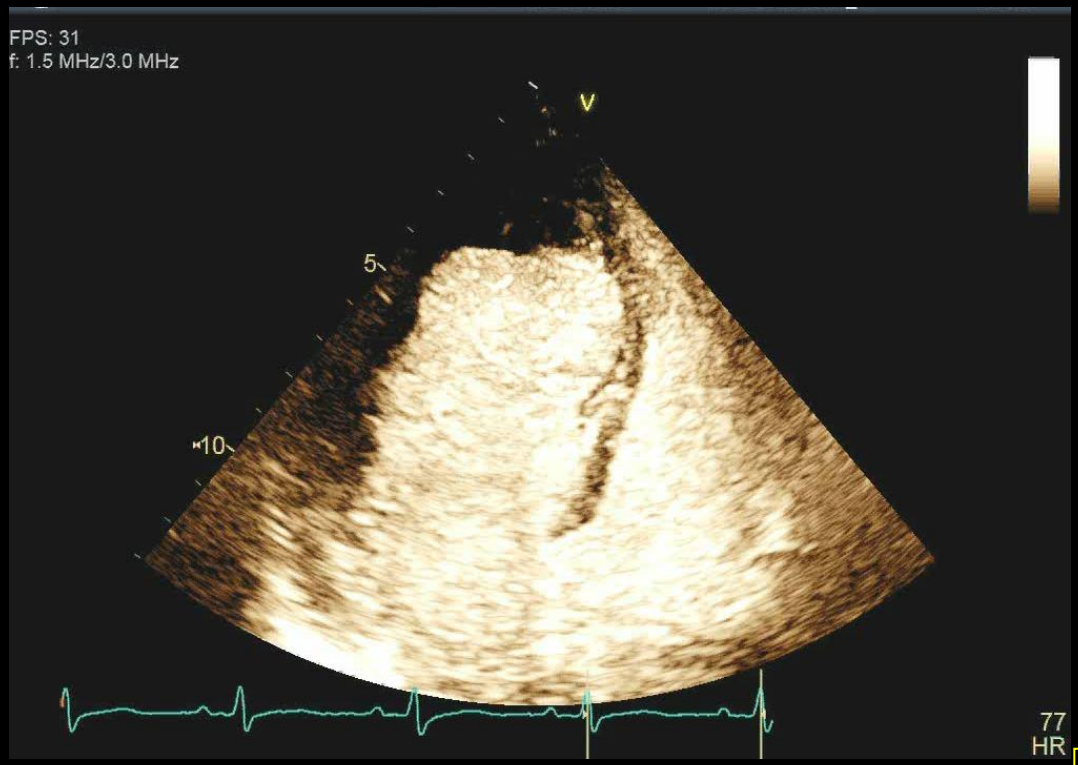



**Apical LAX**

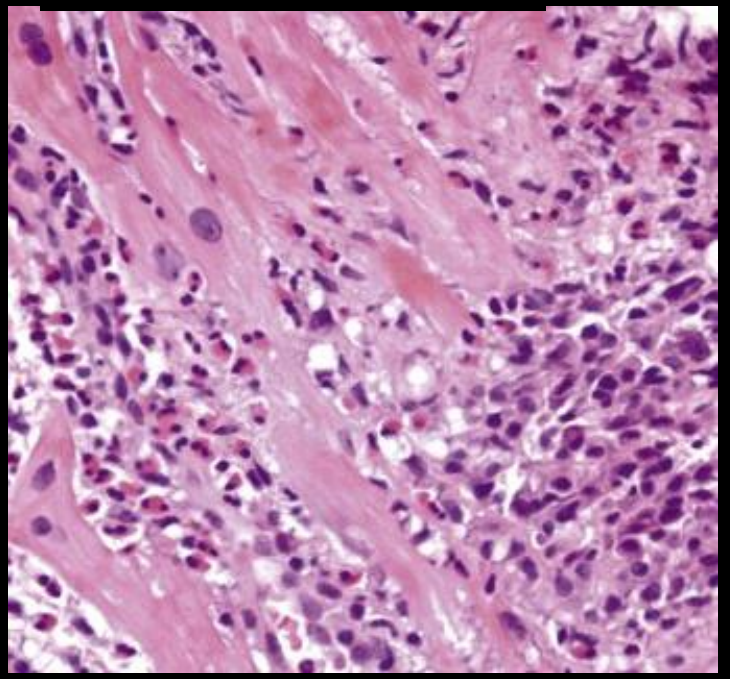



**2-C**

# 34 yo female with headache, chest and jaw pain



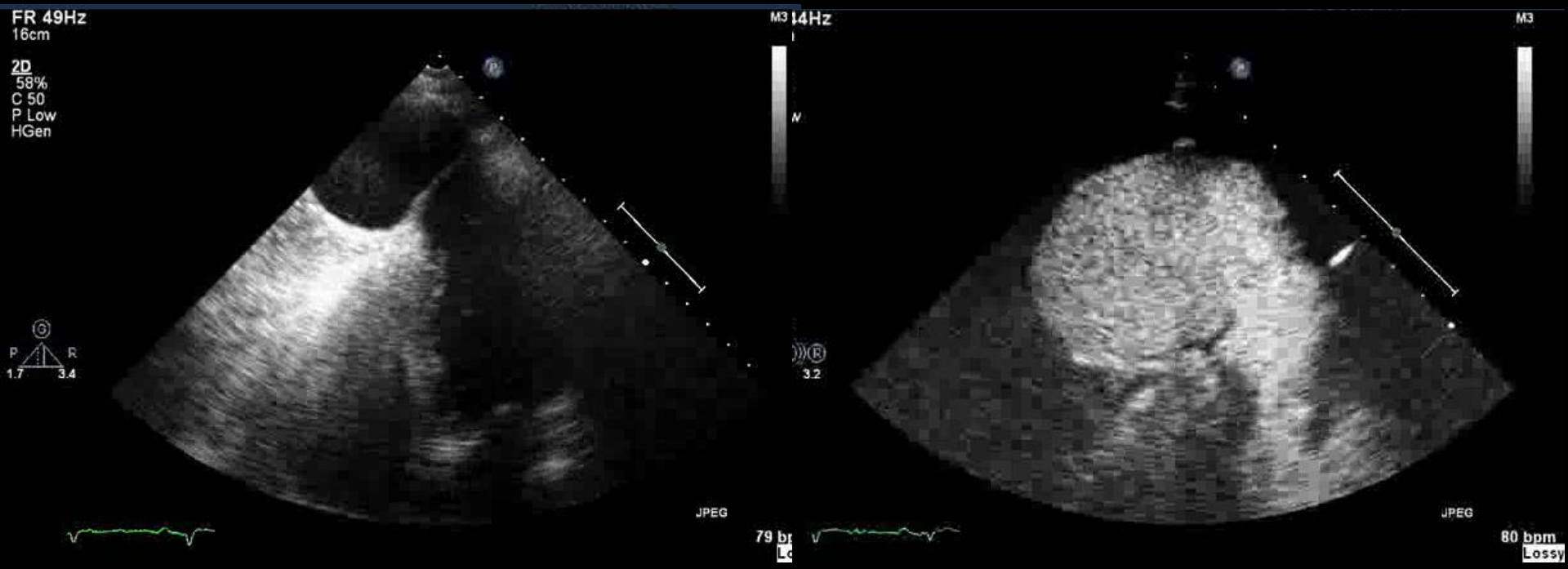

CBC: eosinophilia



RV biopsy: eosinophilic infiltration, degenerating thrombus

Diagnosis:
**Hypereosinophilic Heart Disease**

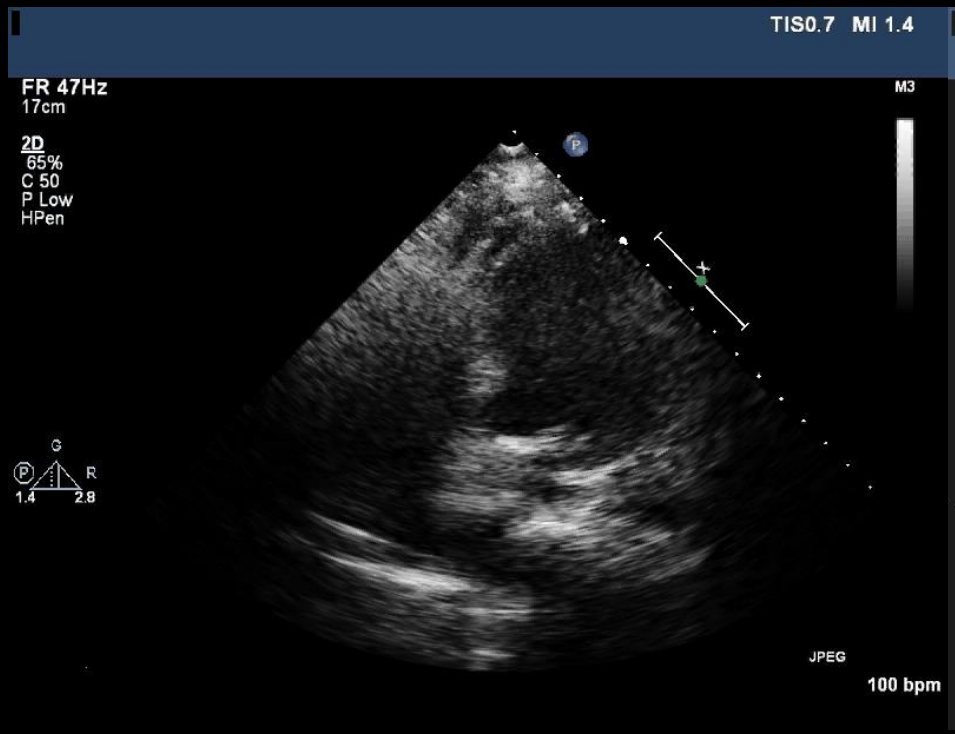
# 72 yo male preop - abnormal CXR on pre-op eval



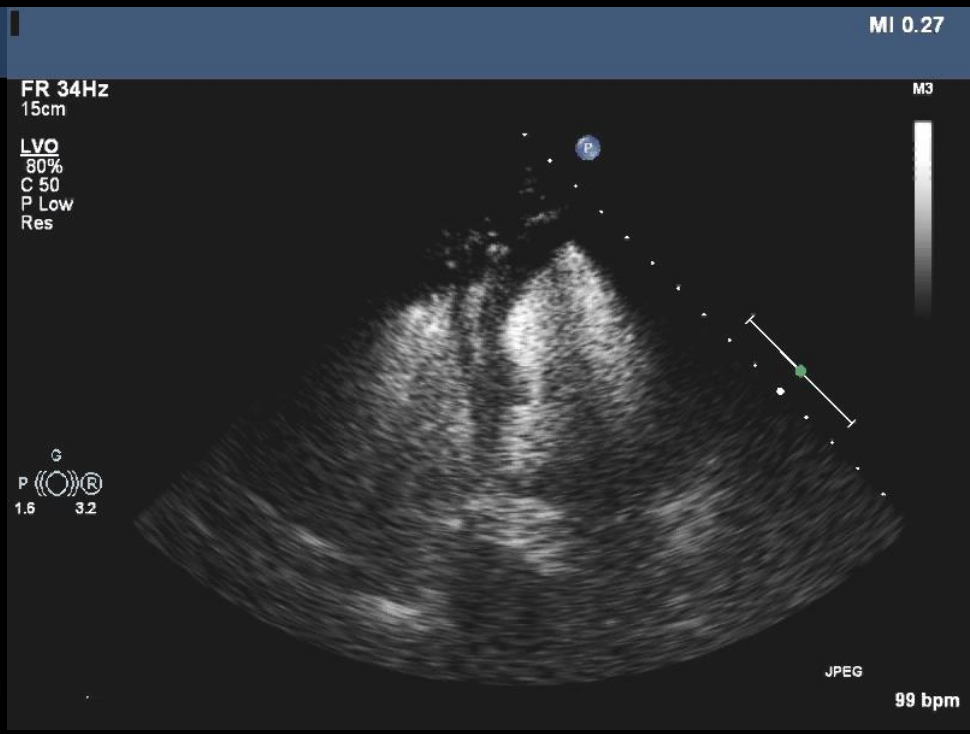

Diagnosis:
"Silent MI" complication – LV apical pseudoaneurysm

Courtesy Dr. Roxy Senior

# 81 yo female s/p transapical TAVR
# Echo prior to discharge:

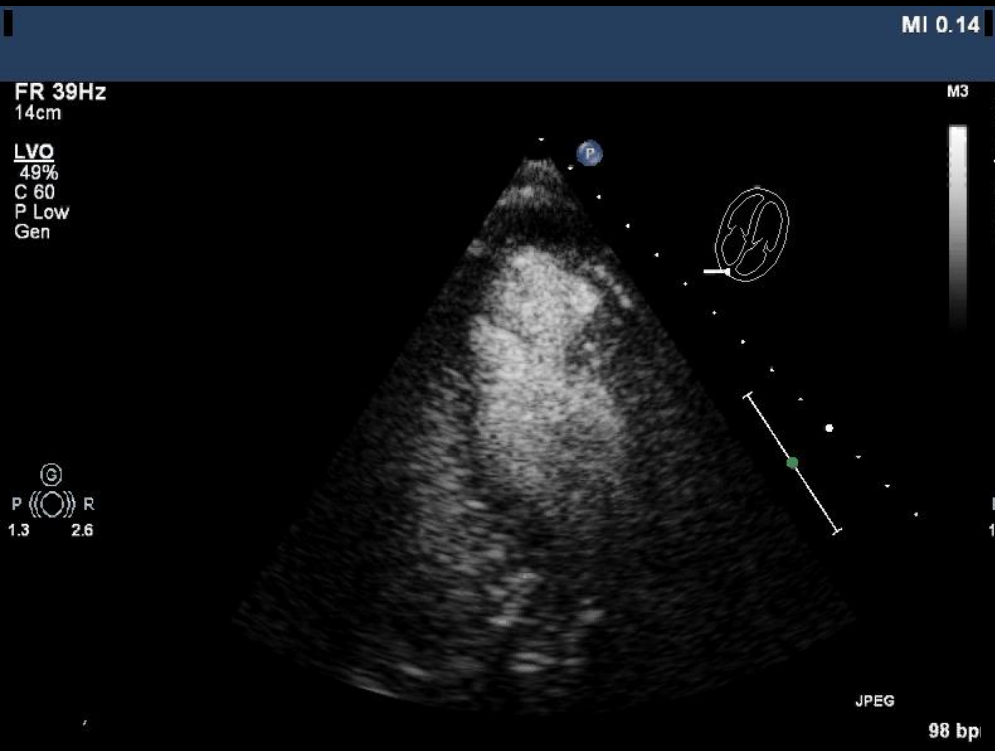



4-C baseline

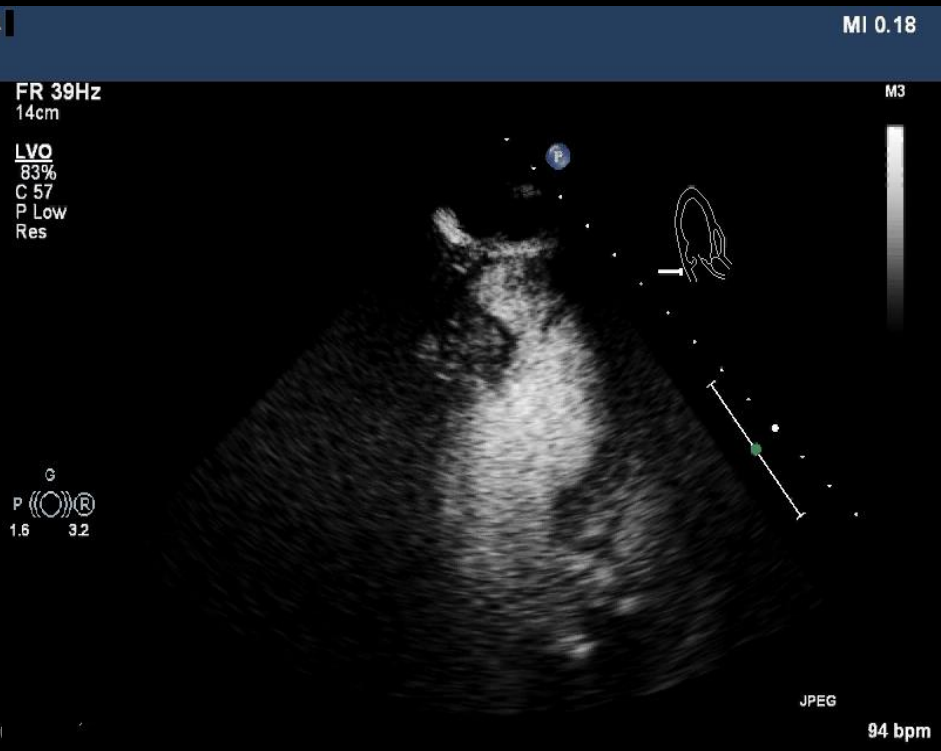



4-C with Contrast

# 81 yo female s/p transapical TAVR: one month follow up - dyspnea




4-C

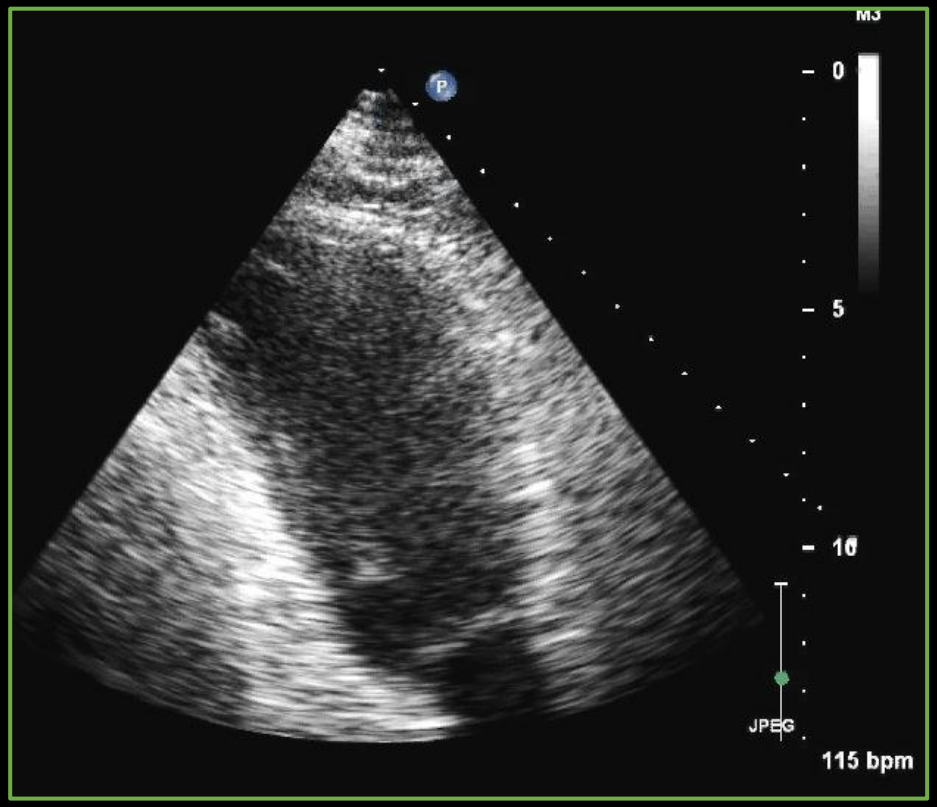



Apical LAX

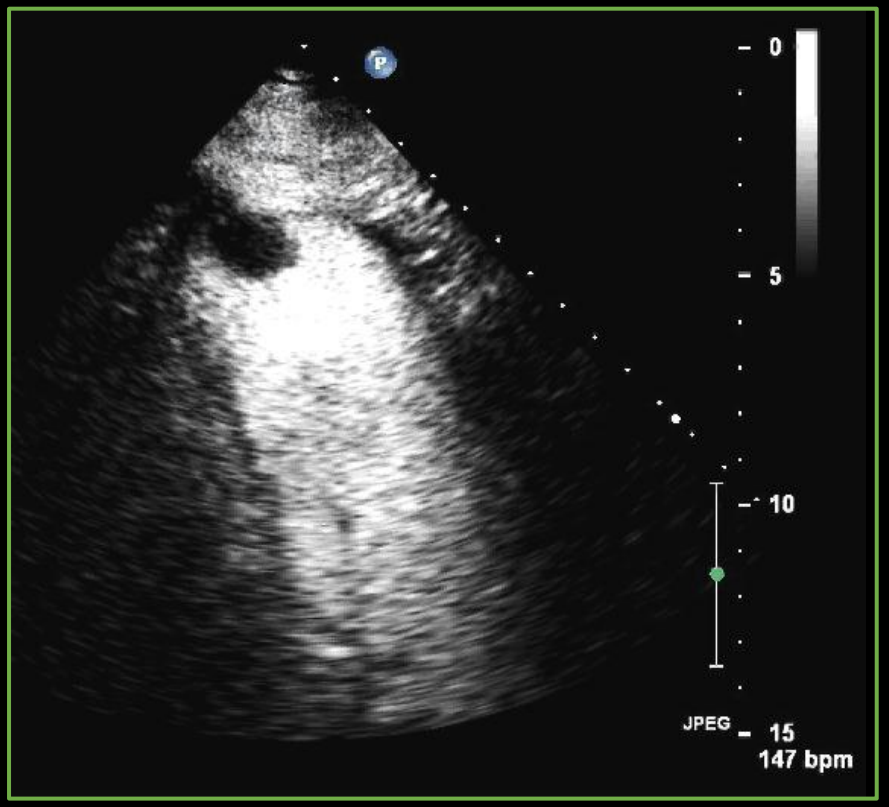
Diagnosis:

TAVR Procedural Complication – LV apical pseudoaneurysm

# 68 yo male s/p anterior MI




2-C




2-C with contrast

## Diagnosis: Post-MI complication – Thrombus

Mulvagh: J Am Soc Echocardiogr 21:1179, 2008

# History of Contrast Echo "Guidelines"

2000

American Society of Echocardiography Consensus Statement on the Clinical Applications of Ultrasonic

2008

ASE CONSENSUS STATEMENT

American Society of Echocardiography Consensus Statement on the Clinical Applications of Ultrasonic

2014

GUIDELINES AND STANDARDS

Guidelines for the Cardiac Sonographer in the Performance of Contrast Echocardiography: A Focused Update from the American Society

2018

GUIDELINES AND STANDARDS

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

Thomas R. Porter, MD, FASE (Chair), Sharon L. Mulvagh, MD, FASE (Co-Chair),

Mulvagh S, JASE 2000; Mulvagh S, JASE 2008; Porter TR JASE 2014; Porter TR JASE 2018

# Indications for UEA's

- Assessment of LV structure and function
- Quantification of LV volumes and EF
- Stress Echo – LVO-RWMA's, *Perfusion, viability*
- Cardiac anatomy – LV apex
  - Apical variant of HCM
  - Ventricular noncompaction
  - Apical thrombus
- MI complications: LV aneurysm, pseudoaneurysm, rupture; post-revascularization
- Intracardiac masses: Tumors and thrombi, (TEE – LAA thrombus)
- Doppler (TR, AS)
- Chest Pain (ED, ICU/CCU-bedside)
- Pediatrics: transplant screening
- Vascular: aortic endografts, dissection; carotid IPN, femoral, PAD
- *Thrombolysis/Molecular/Targeted Imaging*

Mulvagh SL: J Am Soc Echocardiogr 2000
Mulvagh SL: J Am Soc Echocardiogr 2008: 21:1179-201
Porter TR: J Am Soc Echocardiogr 2014: 2014;27:797-810
Porter TR: J Am Soc Echocardiogr 2018: 31;241-274

**Clinical Indication for Study**

**Quality of Images**

*poor* *fair* *good*

Chest pain - angina?

LV Thrombus

Stress echo

ΔLVEF (chemo)

LVEF for ICD or BiV

Dyspnea

Hypotension

Aortic dissect

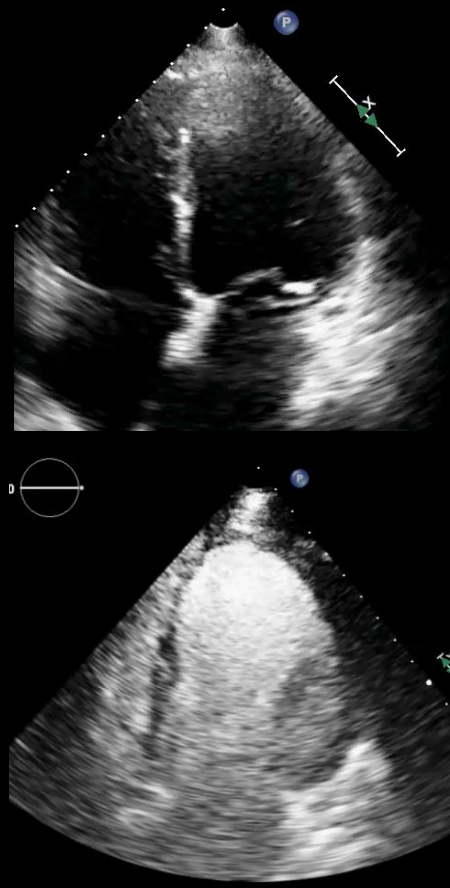
Atrial fib

Valve

Pericardia

**BottomLine:**
***If unable to get the clinical information required to make the relevant diagnosis – use UEA***

**High - Benefit from UCA - Low**



Adaptation Courtesy Lindner JR, From Otto C, Textbook of Clinical Echocardiography, Heart 2015

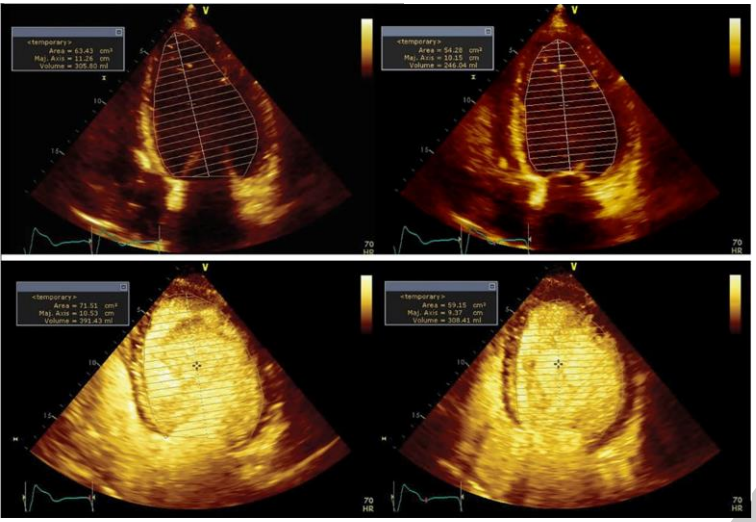
# Contrast for Quantification of LV systolic function & volumes

GUIDELINES AND STANDARDS

Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging

GUIDELINES AND STANDARDS

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



- Contrast-enhanced images may provide larger volumes than unenhanced images
- closer to those obtained CMR in head-to-head comparison
- Decreases variability; increases accuracy
  - *Device implantation*
  - *Serial studies: ChemoRx, VHD*

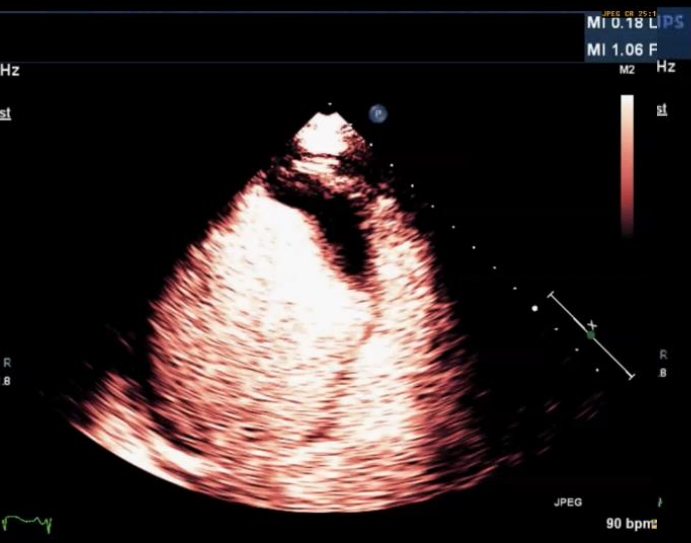

Lang R, J Am Soc Echocardiogr 2015

Mulvagh SL, J Am Soc Echocardiogr 2008

*Porter TR, J Am Soc Echocardiogr 2018*

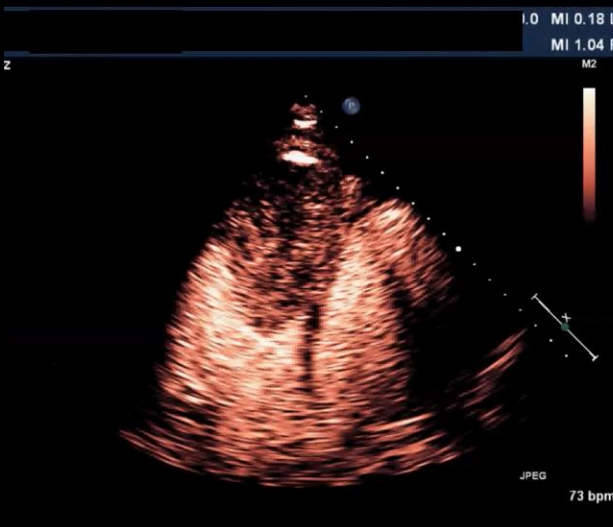
Hoffmann R, J Am Coll Cardiol 2006

# Intracardiac Masses: Detection *& Characterization*




**Diagnosis: Thrombus**


**Myxoma**




**Metastatic Tumor**

Porter TR, Mulvagh SL et al. J Am Soc Echocardiogr 2018 31, 241-274

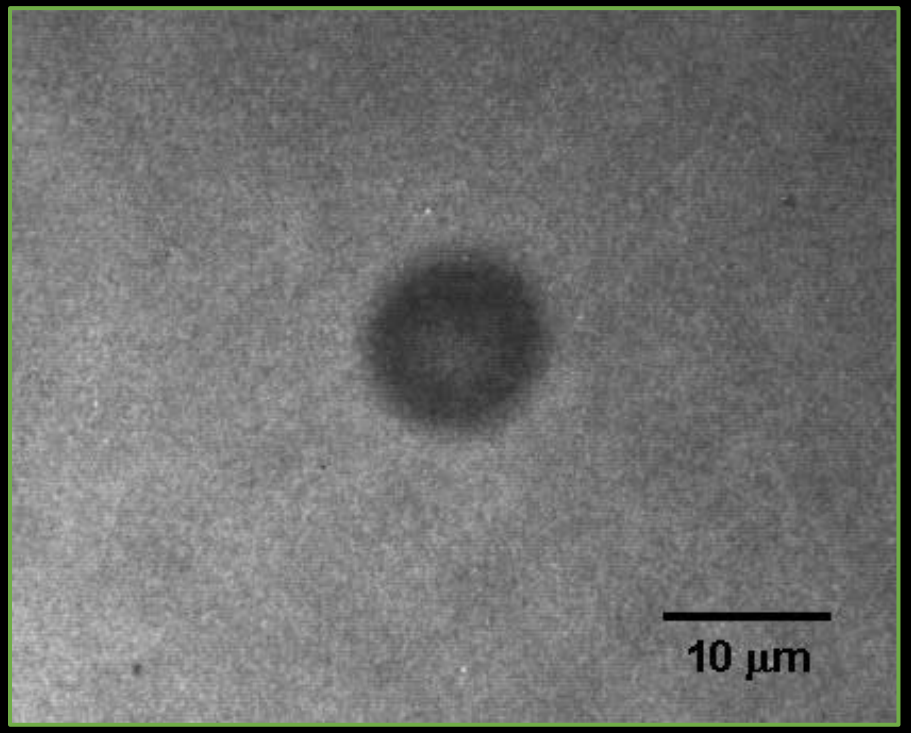
# Microbubbles *Interact* with Ultrasound

"NONLINEAR"

(expand +/- contract)

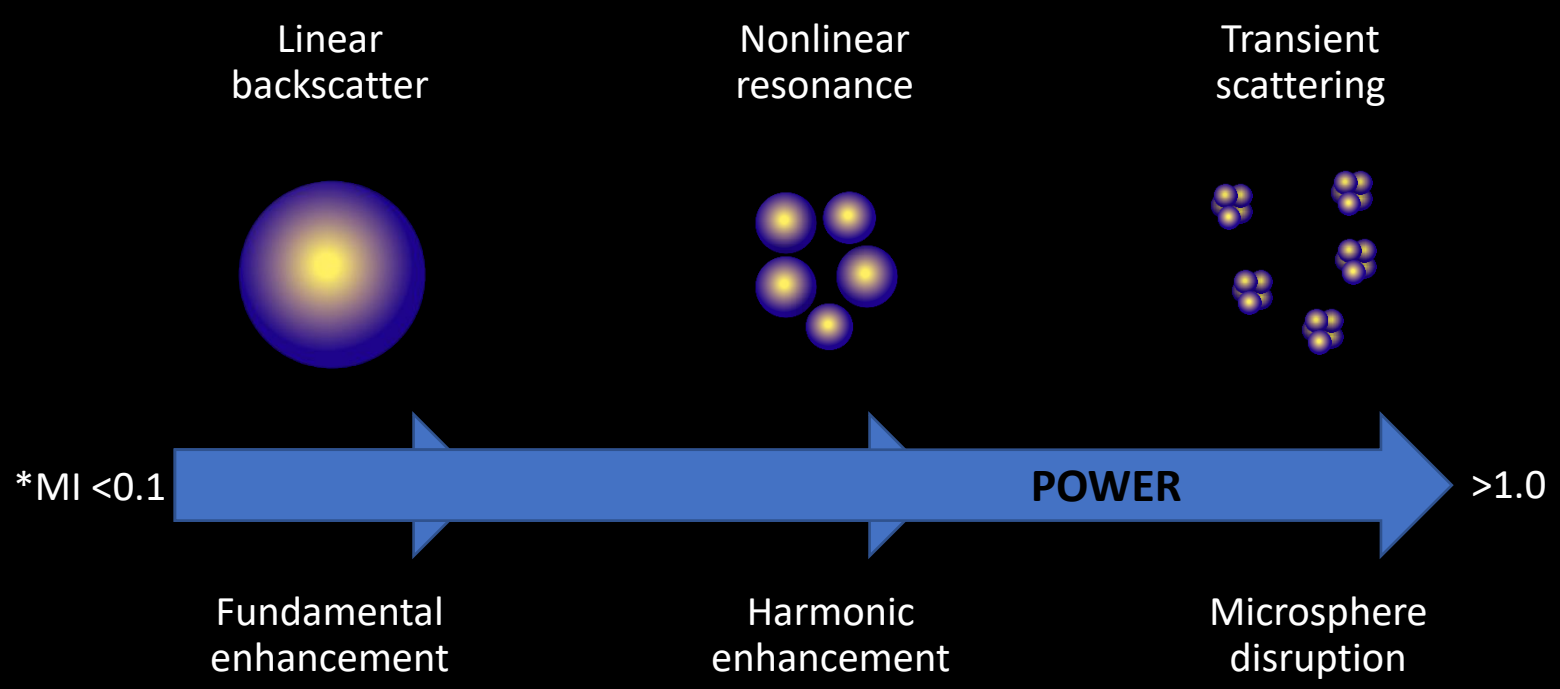
Mechanical Index (MI)

$$MI = \frac{\text{Peak acoustic negative pressure}}{\sqrt{\text{frequency}}}$$




Brandaris camera $25 \times 10^6$ fps, courtesy N deJong, Erasmus University, Rotterdam NL

# Interaction of Ultrasound and Microbubbles

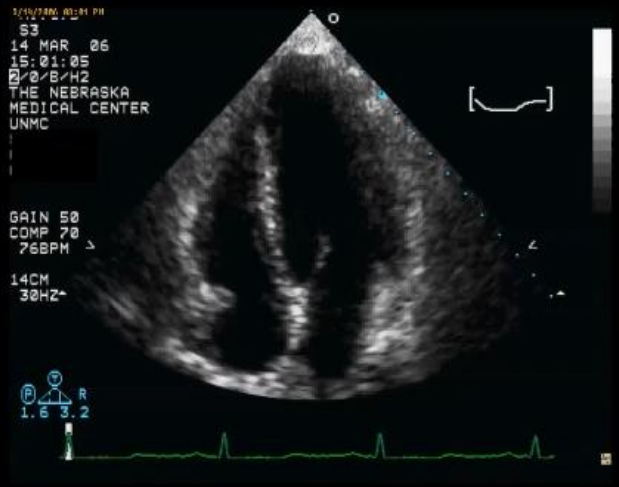



***MI = Mechanical Index**

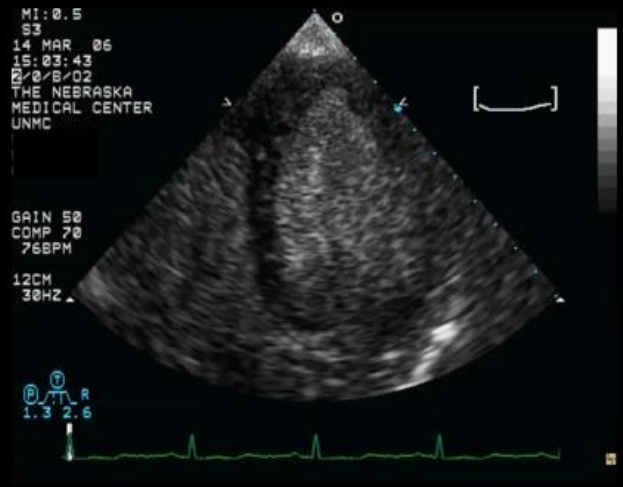
| | |
|---|---|
| **Very Low MI** (VLMI) | [0.1 to < 0.2] |
| **Low MI** | [0.2 to < 0.3] |
| Intermediate MI | [0.3 to 0.5] |
| **High (Flash) MI** | > 0.5 -1.0 |

Burns et al: Diagnostic Ultrasound 1:57, 1998

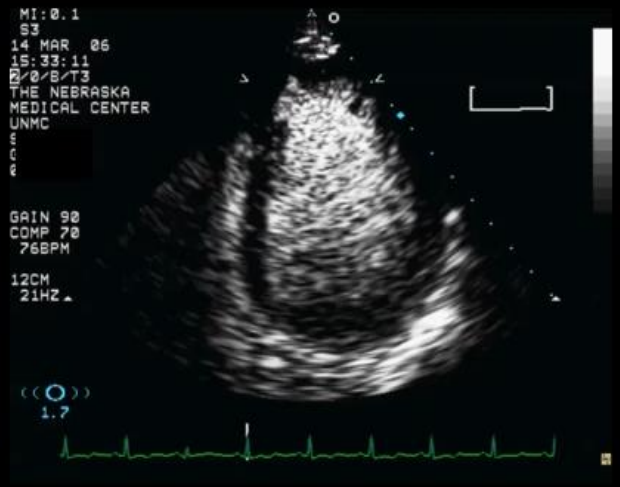
# Optimizing Contrast Images—Use (Very) Low MI




Before contrast
High MI Harmonic



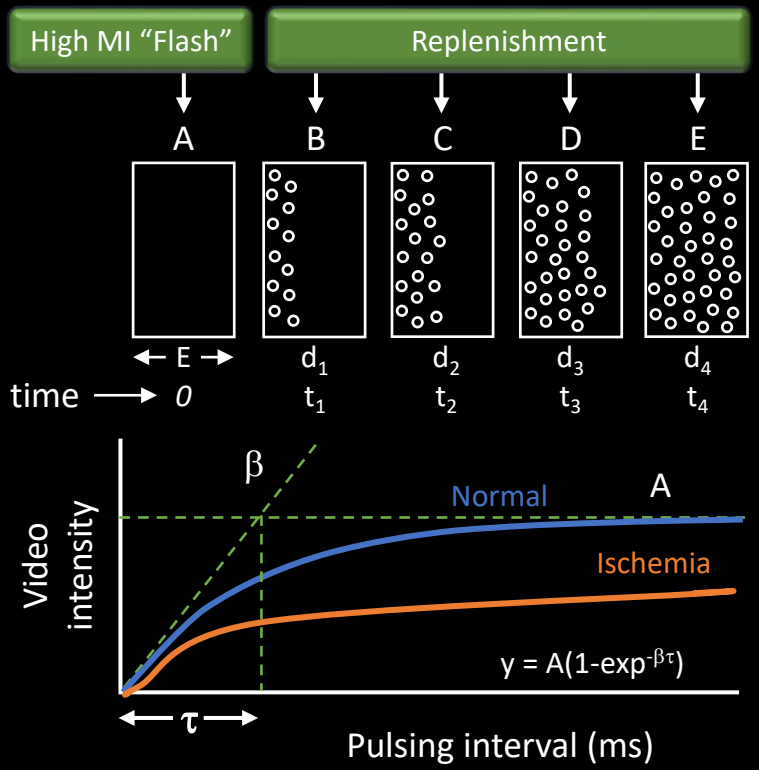

IV Contrast using LVO
Harmonic B-mode 0.5 MI

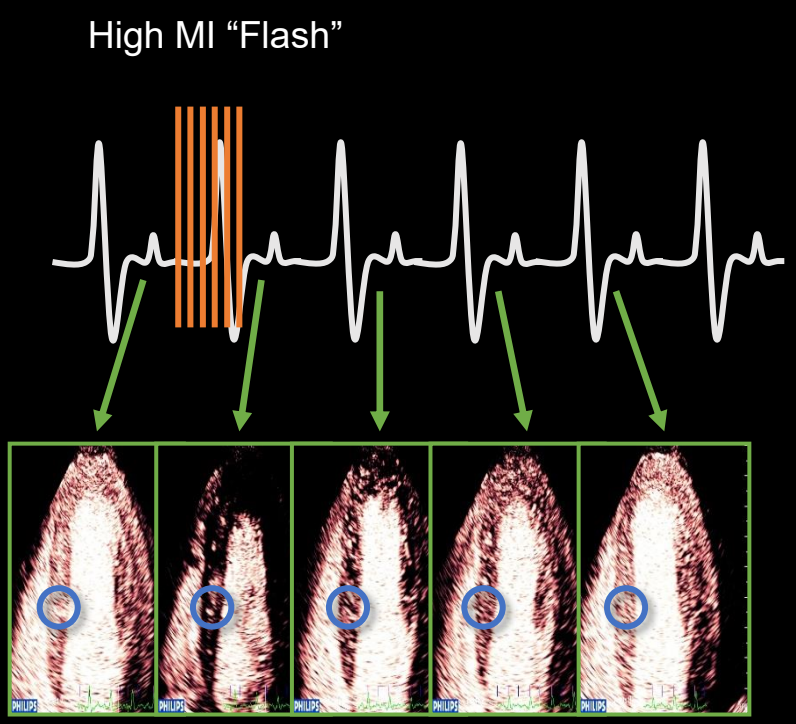



IV Contrast with VLMI
pulse sequence scheme

Porter TR, Mulvagh SL et al. J Am Soc Echocardiogr 2018

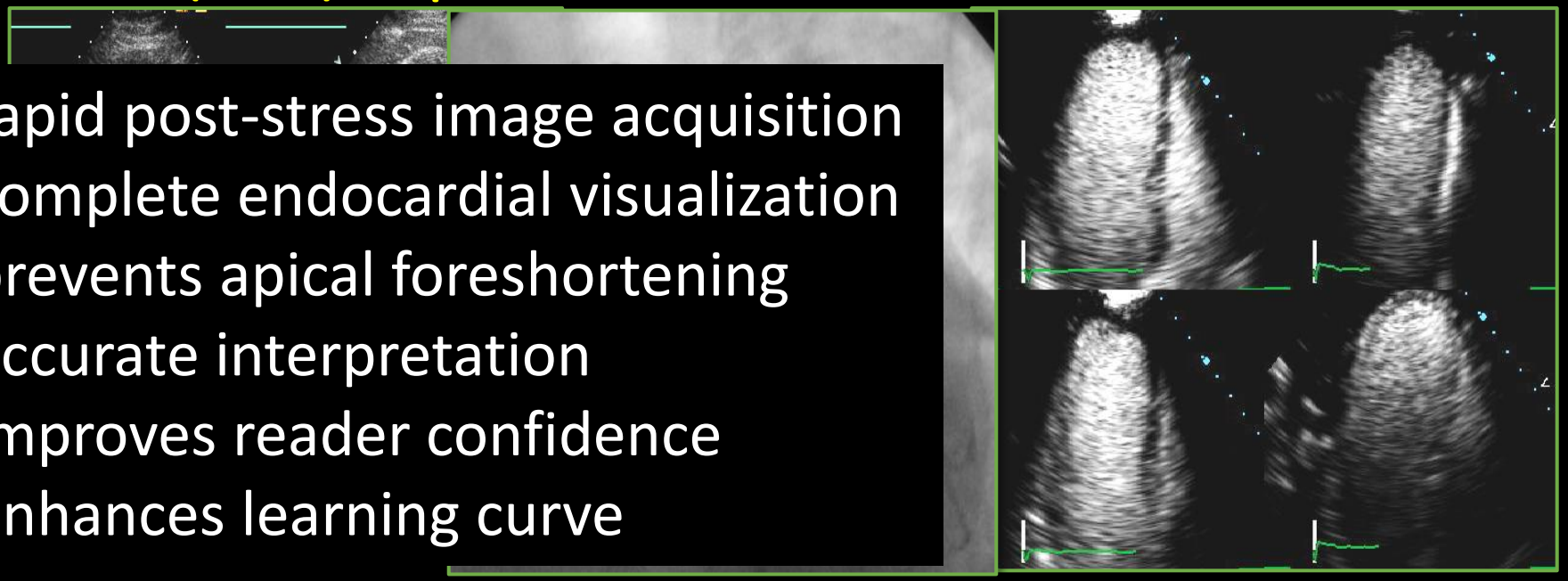
# Very Low MI (VLMI) *Perfusion* Imaging with UEA




Wei K, Kaul S et al: Circulation 98:473, 1998

# Stress Echo:
# Contrast (UEA) improves Endocardial Border Definition

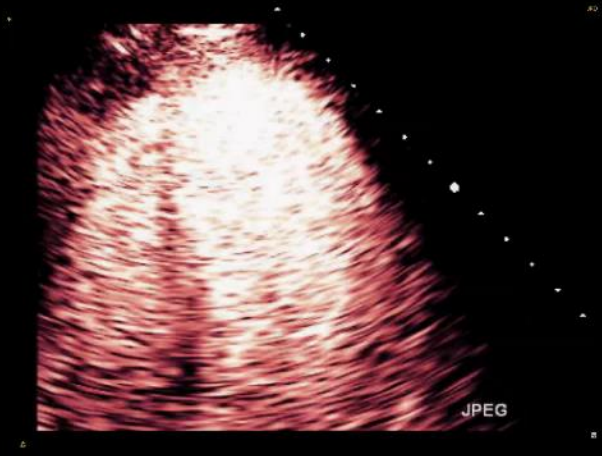


- rapid post-stress image acquisition
- complete endocardial visualization
- prevents apical foreshortening
- accurate interpretation
- improves reader confidence
- enhances learning curve

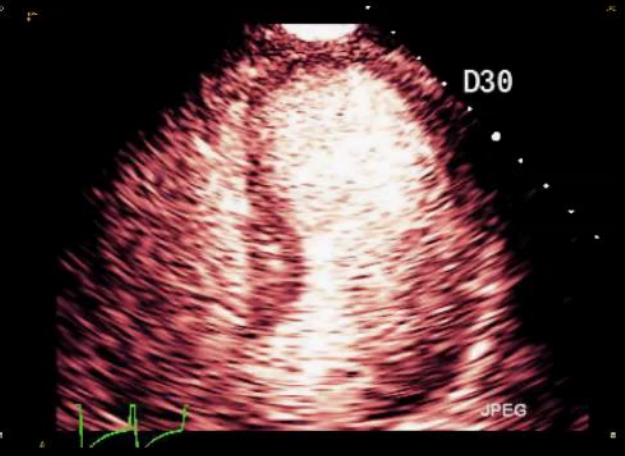
Rainbird: JASE 14:378, 2001; Dolan: AHJ 142:908, 2001;Moir: Circulation 110:1108, 2004; Plana: JACC Img 1:145, 2008

Porter: JACC 23:1440, 1994

# Stress Echo: Myocardial Function *and* Perfusion




A4C rest



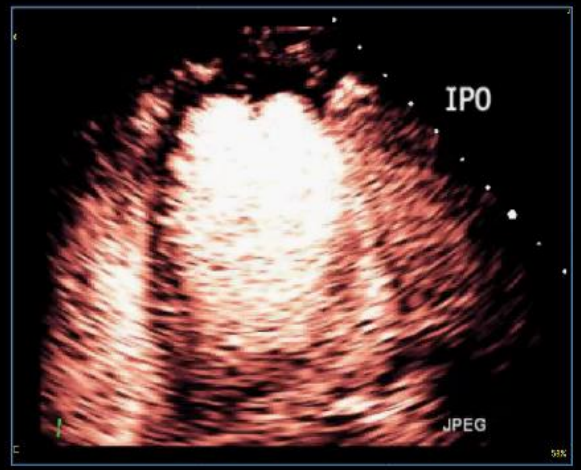

A4C stress

Dobutamine Stress

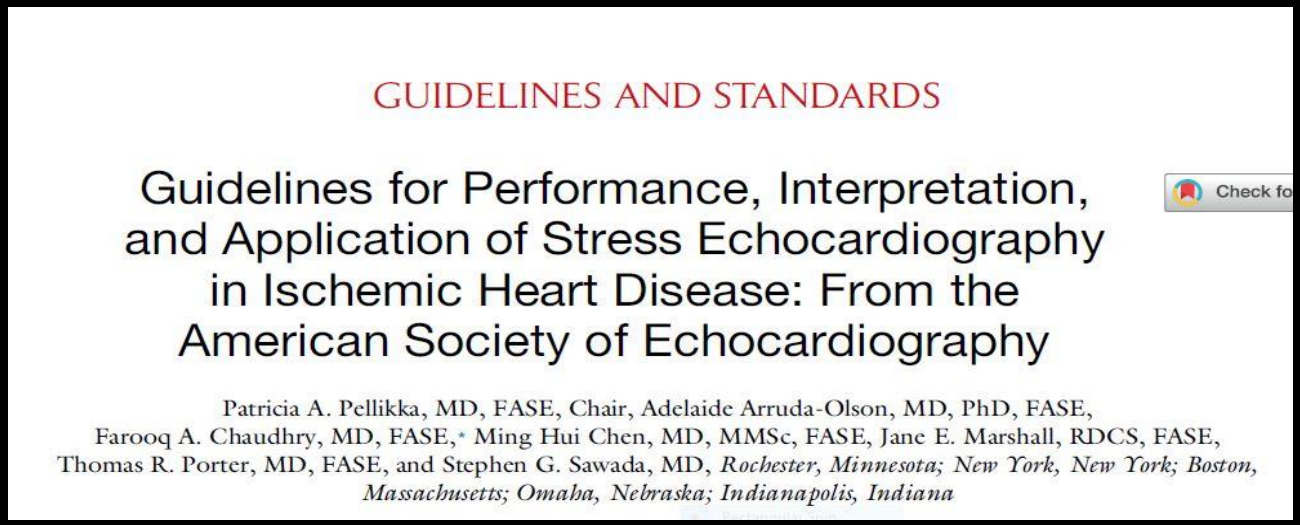
Exercise Stress

**Rest**


**Stress**



# Stress Echo Guidelines



GUIDELINES AND STANDARDS

Guidelines for Performance, Interpretation, and Application of Stress Echocardiography in Ischemic Heart Disease: From the American Society of Echocardiography

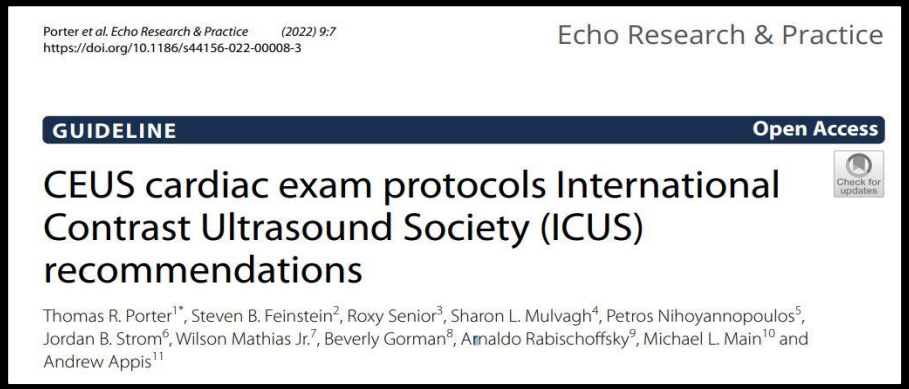
Patricia A. Pellikka, MD, FASE, Chair, Adelaide Arruda-Olson, MD, PhD, FASE, Farooq A. Chaudhry, MD, FASE,* Ming Hui Chen, MD, MMSc, FASE, Jane E. Marshall, RDCS, FASE, Thomas R. Porter, MD, FASE, and Stephen G. Sawada, MD, *Rochester, Minnesota; New York, New York; Boston, Massachusetts; Omaha, Nebraska; Indianapolis, Indiana*

- ✓ > 2 contiguous segments, OR coronary territory not seen
- ✓ low dose (diluted) bolus; or infusion
- ✓ VLMI (<0.2); brief high MI (0.8) flash
- ✓ Perfusion improves:
  - ✓ sensitivity (DSE, vasodilator)
  - ✓ prognostic value ( bike, DSE, vasodilator)

Pellikka PA et al. J Am Soc Echocardiogr. 2020

# Contrast Echo Perfusion Technique

App



Porter *et al. Echo Research & Practice* (2022) 9:7
https://doi.org/10.1186/s44156-022-00008-3

Echo Research & Practice

GUIDELINE Open Access

CEUS cardiac exam protocols International Contrast Ultrasound Society (ICUS) recommendations

Thomas R. Porter[1*], Steven B. Feinstein[2], Roxy Senior[3], Sharon L. Mulvagh[4], Petros Nihoyannopoulos[5], Jordan B. Strom[6], Wilson Mathias Jr.[7], Beverly Gorman[8], Arnaldo Rabischoffsky[9], Michael L. Main[10] and Andrew Appis[11]

- ***Same settings used as for optimal LVO/EBD:***
  - ***very low MI*** (0.12 – 0.20)
  - slow infusion (hand/pump) of microbubbles

- **Additional Step: Flash/Replenishment**
  - brief high (0.8-1.0) MI exposure (“flash”) to deplete myocardium

  - observe replenishment over subsequent cardiac cycles:
    - Rate (velocity, flow), Plateau (blood volume)
      - **Normal = REST: within 4-5 STRESS: within 2**
      - Abnormal = absent, or delayed

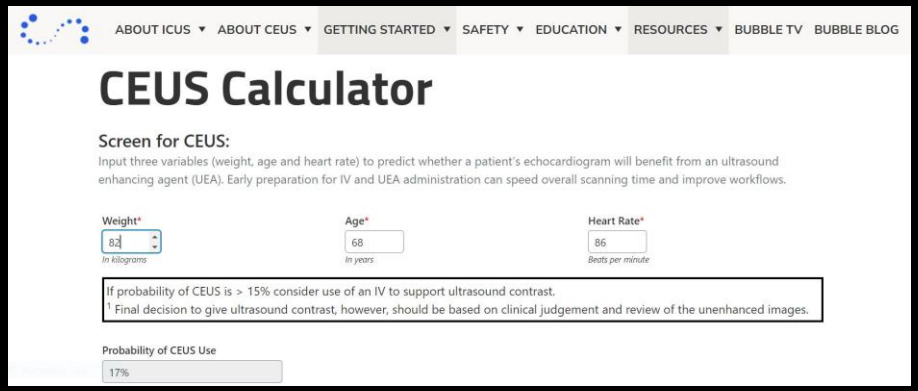
# Best Practices for successful use of Contrast

- ✓Have a standing order for contrast administration
- ✓Enable sonographers to make decision to give and administer
- ✓Train and enable sonographers to place IV's
- ✓Have a physician/sonographer advocate

*Practical Tips for workflow optimization:*

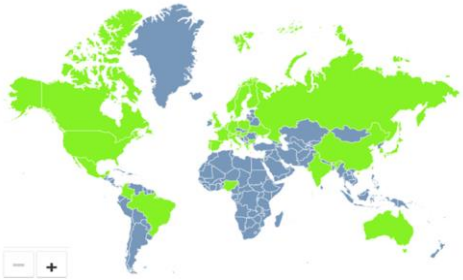
*-Start with APICAL views*

*-Use a "decision aide" "prediction tool" (age, kg, HR)*




https://icus-society.org/ceus-calculator/

ICUS
International Contrast Ultrasound Society



# About ICUS

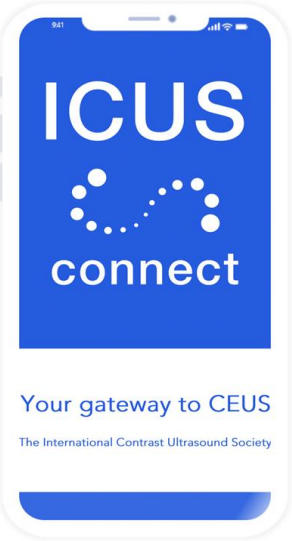
## "International Contrast Ultrasound Society"

### *A non-profit, global professional society solely focused on CEUS*

- ✓ Physicians, sonographers, nurses, scientists, industry, patients
- ✓ Radiology, cardiology, hepatology, vascular and GI medicine, and more

### *No fees – for anything!*

- ✓ **Free ICUS membership**
- ✓ **Excellent website:** ***www.ICUS-Society.org***
- ✓ **Free CME** – Watch on your smart phone or desktop – **WEBINARS** galore!!
- ✓ **Free mobile app, "ICUS Connect"** – CEUS webinars, clinical protocols & resources, billing info, vendor contacts, Bubble TV, Bubble Blogs, Case of the Day - and more!
  - ✓ (get it in your app store – both Apple and Android are supported)
- ✓ **Free CEUS News Monitors** - The latest CEUS trends & developments worldwide!




➢ ***www.ICUS-Society.org***

**X/Twitter – @icus_society**

➢ ***ICUS CONNECT*** *- the free ICUS mobile app*

*CEUS = "contrast enhanced ultrasound" for cardiac and body imaging

**Apple**

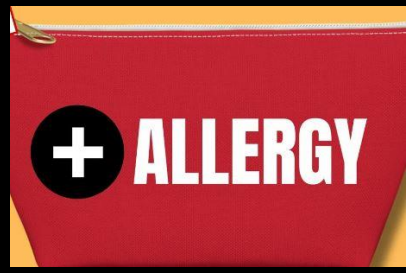
**Android**

# Contrast Echo – Safety

## Recommendations Regarding the Safety of UEAs

1. Abundant literature (see Tables 1 and 2) exists supporting the safety of UEA use in nonpregnant adults. These are supported by FDA modifications in the black-box warning since the 2008 ASE contrast consensus statement (Table 6).
2. Although anaphylactoid reactions are rare, laboratories that routinely use UEAs should have policies in place for emergent resuscitation of patients who may experience serious side effects.
3. UEAs can safely be used in patients with pulmonary hypertension and with right-to-left shunts (COR I, LOE B-NR).

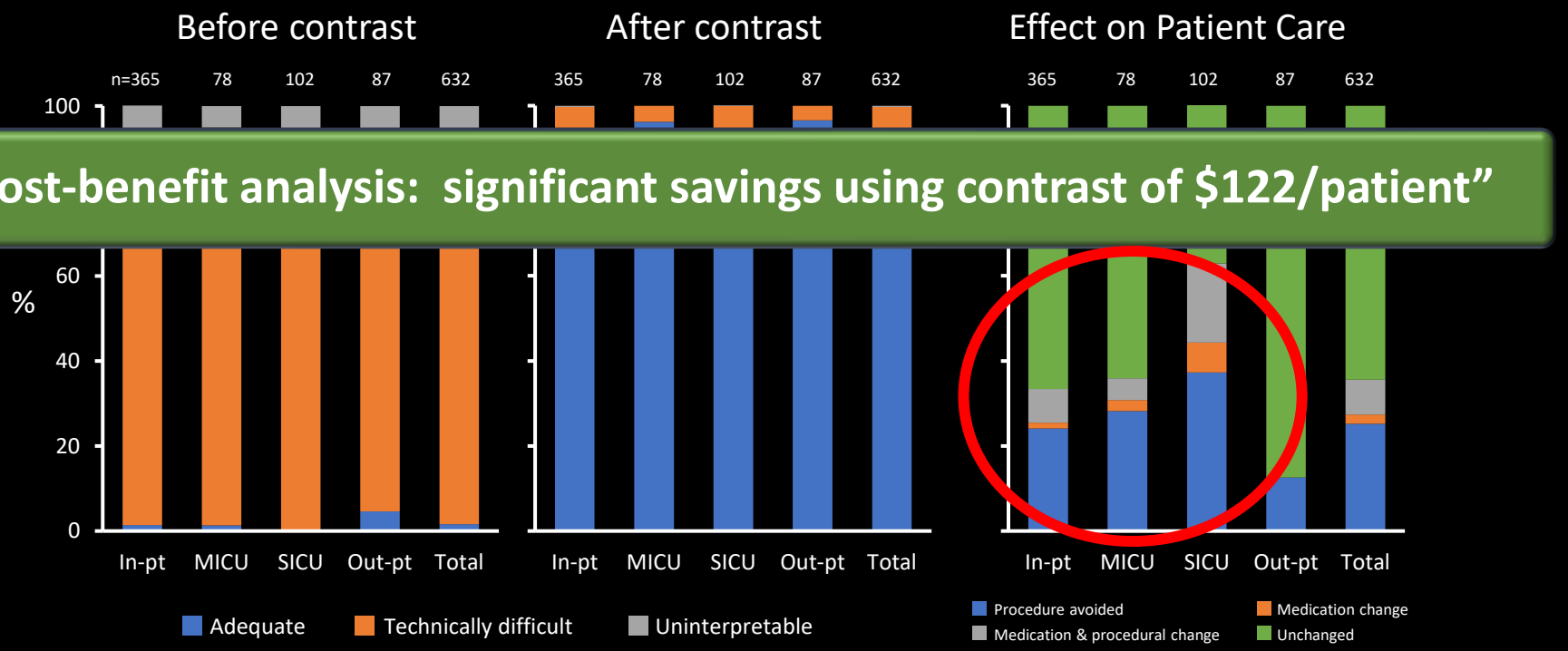
- **Life threatening reactions to UEA are rare (<1:10,000)** (< contrast agents used in other imaging modalities)
- *Labs should develop policies and procedures for early recognition/Rx of serious anaphylactic reactions and have appropriate emergency resuscitation available*




**Only contraindication now is:**

- Known hypersensitivity to contrast agent or ingredients
- Be aware of PEG hypersensitivity potential with lipid-based UEA

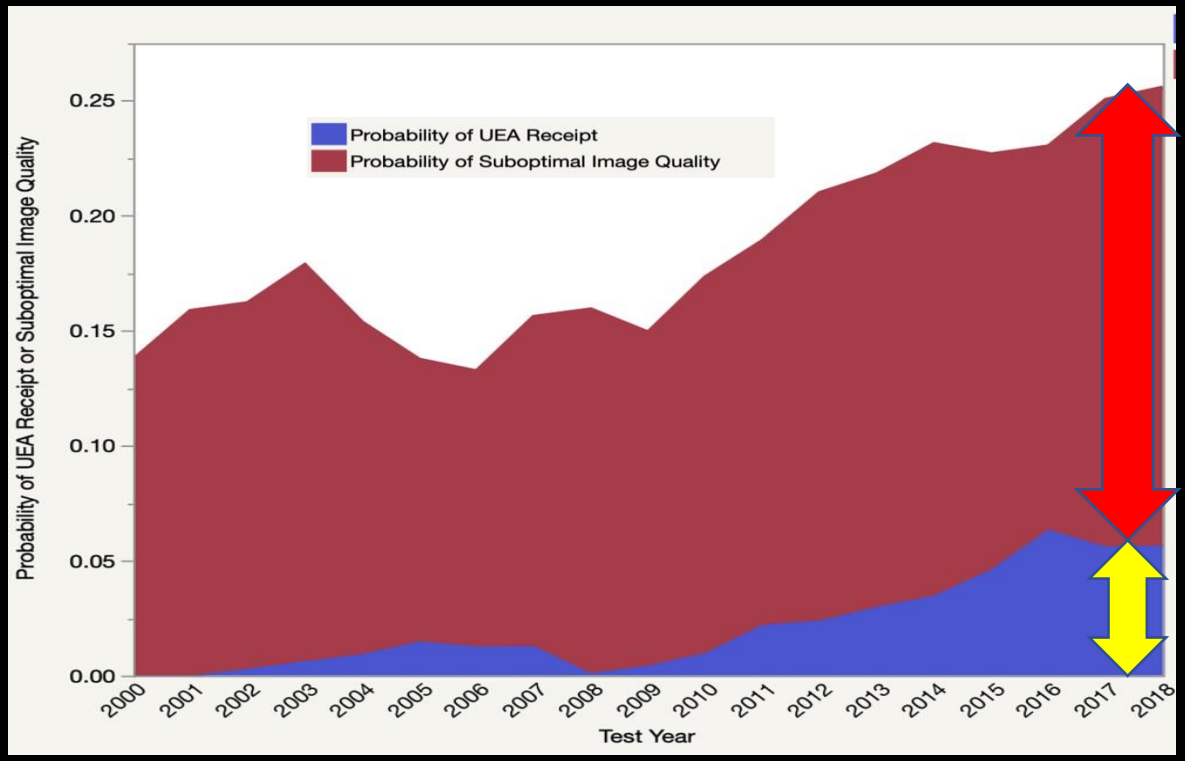
# Impact of Contrast




**"Cost-benefit analysis: significant savings using contrast of $122/patient"**

Kurt et al: JACC 53:802, 2009

# Identification of Need for UEA Study (IN-USE Study)




**171,509 TTE**

- **UEA use: 4%**
- **Suboptimal studies: 23%**
- **Less use in women**

**Predictors for Suboptimal Image Quality/ UEA use :**

- ***older age***
- ***weight***
- ***heart rate***

**UEA underutilization despite Need-Predictors: increased age, BMI, HR – Development and Validation of prediction tool**

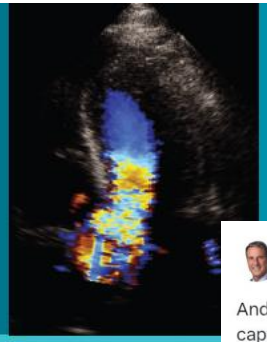

Fraiche AM et al. J Am Soc Echocardiogr 2020 331500-1508
Lehenbauer KR et al. J Am Soc Echocardiogr 2022 PMID 352475553

# Take Home Points: Contrast Echo

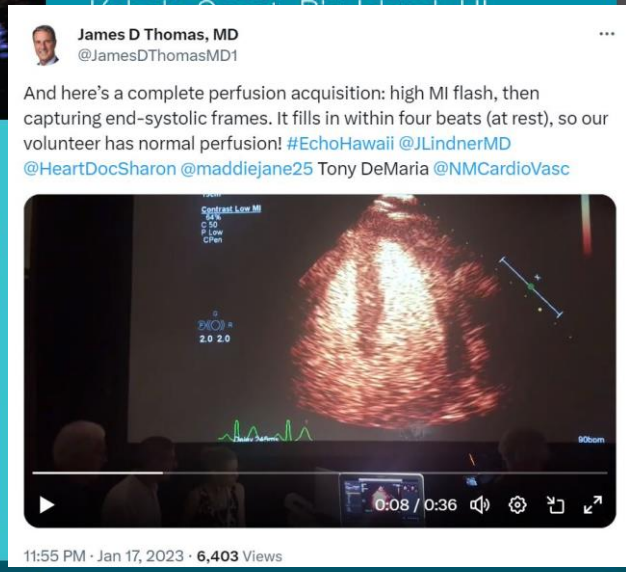
- is essential to contemporary echo practice
- is necessary when images are suboptimal
- provides incremental diagnostic information
- is optimized by understanding microbubble and ultrasound interaction
- is safe, portable, non-ionizing and cost-effective

33rd ANNUAL

# ECHO HAWAII



**January 15–19, 2024**
Fairmont Orchid




**Course Director**
Jonathan R. Lindner, MD, FASE
Past President, ASE

**Course Co-Director**
Sharon L. Mulvagh, MD, FASE
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ASE American Society of Echocardiography
Sound Saves Lives

**Contrast Echo Workshop:**
https://twitter.com/i/status/1615558380550246402

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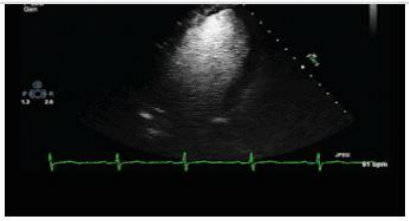


Courtesy of Thomas R. Porter, MD & Linda D. Gillam, MD.

Home | Live Meetings | Self-learning Activities | Webinars | Protocols | Resources | My Programs


## *Self-learning Activity*

**Activity:** Ultrasound Enhancing Agents: Optimizing Echocardiography in Children and Adults

**Audience:** For all physicians with an interest in cardiac imaging (including but not limited to cardiologists, interventional cardiologists, cardiac, thoracic, and vascular surgeons, and radiologists), sonographers, and specialty nurses involved with echocardiography

**Physician and Nurses Provider:** Medical Education Resources
**Credit:** 1 *AMA PRA Category 1 Credit*™ & 1 ANCC Contract Hour
**Original Release Date:** November 2020
**Re-review Date:** November 2022
**Expiration Date:** November 2024

**Sonographer Provider:** Society of Diagnostic Medical Sonographers
**Credit:** 1 SDMS CME Credit
**Release Date:** November 27, 2022
**Expiration Date:** November 27, 2023

Launch Program

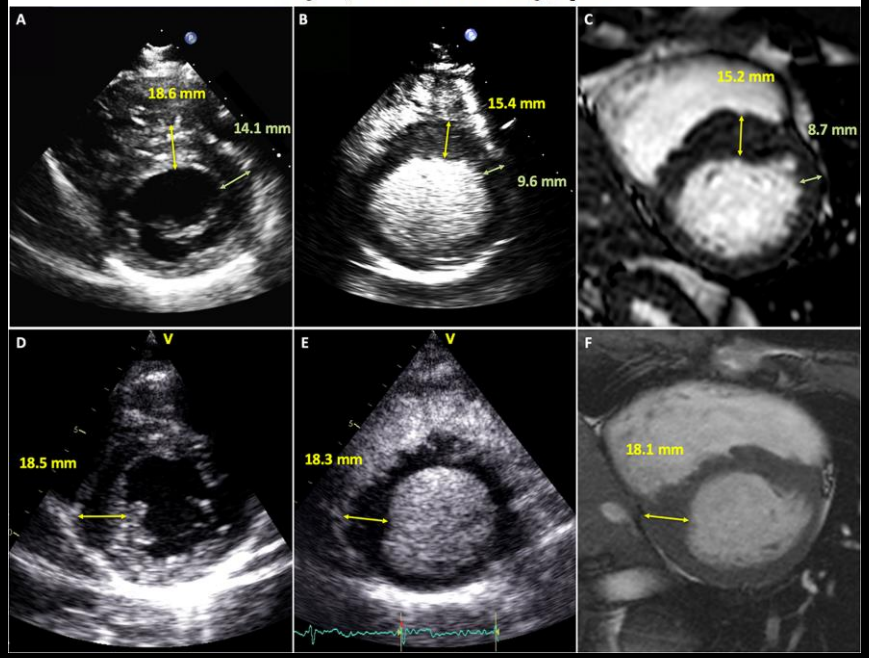
https://www.enhancedecho.com


Thank You!
smulvagh@mayo.edu
@HeartDocSharon

HYPERTROPHIC CARDIOMYOPATHY AND CONTRAST ECHOCARDIOGRAPHY

## Contrast-Enhanced Echocardiographic Measurement of Left Ventricular Wall Thickness in Hypertrophic Cardiomyopathy: Comparison with Standard Echocardiography and Cardiac Magnetic Resonance

Jose Angel Urbano-Moral, MD, PhD, Ana Maria Gonzalez-Gonzalez, MD, PhD, Giuliana Maldonado, MD, Laura Gutierrez-Garcia-Moreno, MD, Ricardo Vivancos-Delgado, MD, Manuel De Mora-Martin, MD, PhD, Jose Fernando Rodriguez-Palomares, MD, PhD, and Arturo Evangelista-Masip, MD, PhD, *London, United Kingdom; and Barcelona and Malaga, Spain*




# HCM + UEA ~ CMR

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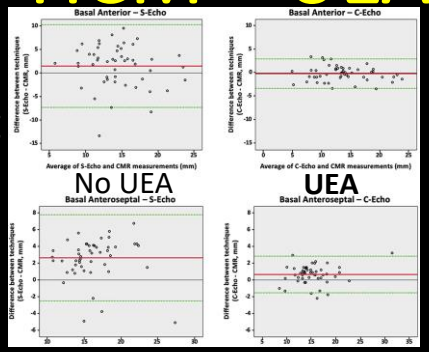
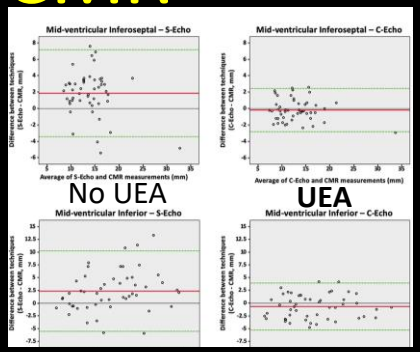
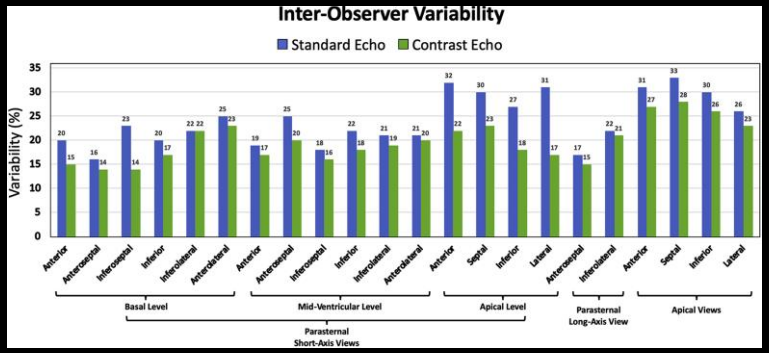



- UEA improves LVWT (mm) – SAX best
- more accurate, *better reproducibility*
- *alternative whenever CMR not available*




Urbano-Moral JA et al. J Am Soc Echocardiogr 2020;33:1106

# Contrast-Enhanced Anatomic Imaging as Compared to Contrast-Enhanced Tissue Characterization for Detection of Left Ventricular Thrombus

Jonathan W. Weinsaft, MD,*† Raymond J. Kim, MD,‡ Michael Ross, MD,*

- **121 "high-risk" patients: MI or CHF**
- **DE-CMR was gold standard**

**Table 3. Diagnostic Performance of Anatomic Imaging for LV Thrombus***

| | Sensitivity | Specificity | Accuracy | Positive Predictive Value | Negative Predictive Value |
|---|---|---|---|---|---|
| Noncontrast echocardiography | 33% (8/24) | 94% (91/97) | 82% (99/121) | 57% (8/14) | 85% (91/107) |
| Contrast echocardiography | 61% (14/23)‡ | 99% (96/97) | 92% (110/120)§ | 93% (14/15) | 91% (96/105) |
| Cine-CMR | 79% (19/24)† | 99% (96/97) | 95% (115/121)† | 95% (19/20) | 95% (96/101) |

- ***Those missed by Contrast Echo and Cine CMR were small and sessile***

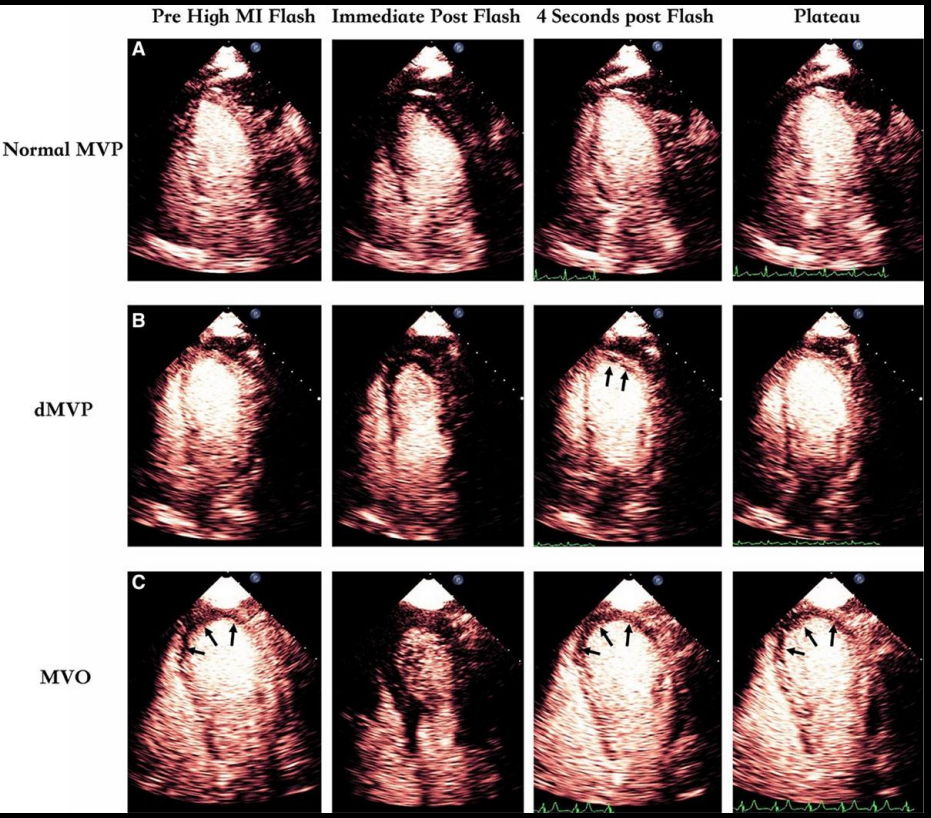
*Weinsaft JW, J Am Coll Cardiol Img 2009;2:969–79*

# Post-PCI Assessment of Microvascular Obstruction

Circulation: Cardiovascular Imaging

ORIGINAL ARTICLE

**Event-Free Survival Following Successful Percutaneous Intervention in Acute Myocardial Infarction Depends on Microvascular Perfusion**



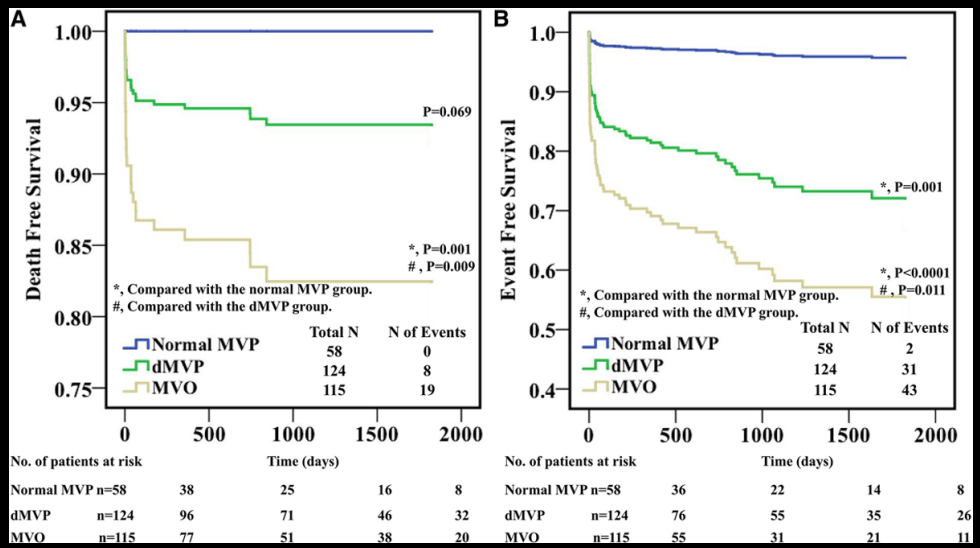

**~300 STEMI pts, PCI: TIMI 3; MCE w/in 48 hrs**

-***delayed microvascular flow (42%)***-dMVP
-***microvascular obstruction (39%)*** -MV

**Follow-up:** 3 month: worse EF in MVO

5 yrs: ***both dMVP and MVO***

- independent predictors of adverse events



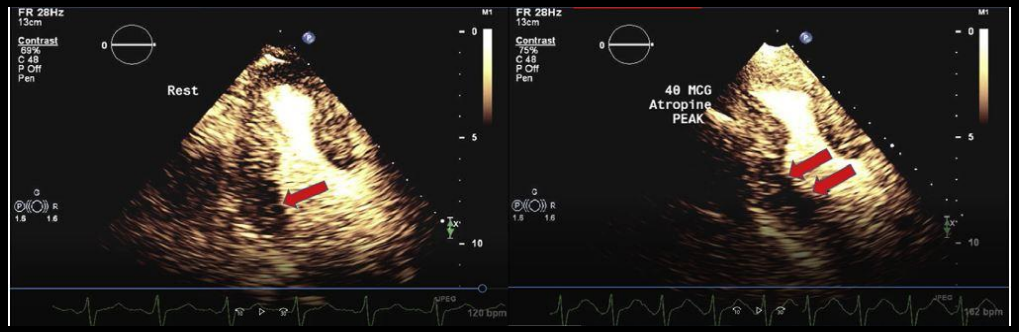

Xie F, et al. Circ Cardiovasc Imaging2020

# DSE Contrast Perfusion for Pediatric Heart Transplant Screening for CAV

ARTICLE IN PRESS

Feasibility of Real-Time Myocardial Contrast Echocardiography to Detect Cardiac Allograft Vasculopathy in Pediatric Heart Transplant Recipients

Nowell M. Fine, MD, SM, Steven C. Greenway, MD, MSc, Sharon L. Mulvagh, MD, Runqing Huang, PhD, Shalon A. Maxon, RN, Mary J. Hepinstall, RN, Jason H. Anderson, MD, and Jonathan N. Johnson, MD, *Calgary, Alberta, and Halifax, Nova Scotia, Canada; and Rochester, Minnesota*



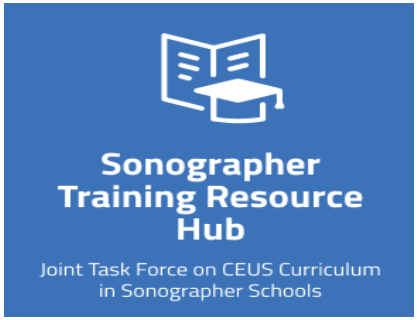

| | Overall | No CAV | CAV |
|---|---|---|---|
| MBFR | 3.4 ± 0.7 | 3.7 ± 0.8 | 2.0 ± 0.2 |

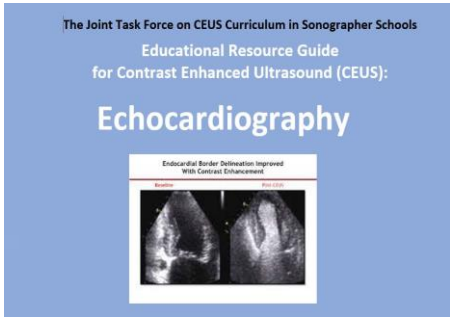
Fine N et al. J Am Soc Echocardiogr 2021

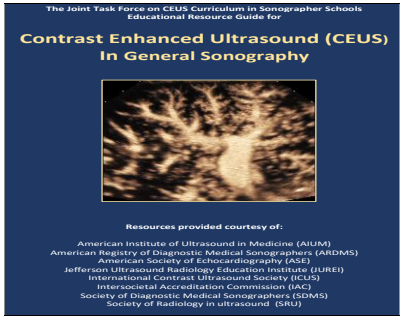
- CAV causes significant morbidity in pediatric heart tx recipients
  - difficult to detect by conventional noninvasive techniques
- RTMCE during DSE: n=36 (10-21yo)
  - was feasible and safe
- Perfusion analysis identified CAV (n=5) when compared w/ ICA
  - Accuracy 89%; spec 94%; sens 60%
- **RTMCE may be an approach to CAV screening in pediatric heart tx pts**

# Sonographer Training Resource Hub:
## *Free CEUS training tools for sonographer educators*

- Scalable, “plug and play” curriculum resource modules for sonography training
- Links to product labels, webinars, reference materials
- Developed by ICUS Joint Task Force:  AIUM, ARDMS, ASE, ICUS, IAC, SDMS




https://icus-society.org/

# UEA's: Emerging Applications

Table 7 Emerging applications of UEAs

| | Microbubbles required | Ultrasound instrumentation required | Specific applications |
|---|---|---|---|
| Thrombolysis | Commercially available/targeted | Intermittent diagnostic high-MI impulses | Acute coronary syndromes, ischemic stroke |
| Molecular imaging | Targeted/phosphatidyl serine–bearing commercial microbubbles* | High-MI imaging after blood pool clearance | Ischemic memory imaging<br>Plaque inflammation<br>Early plaque formation<br>Myocarditis/transplant rejection |
| Targeted drug/gene delivery | Commercially available/targeted | Intermittent diagnostic high-MI impulses following bolus injection | DNA/RNA delivery for atherosclerosis, limb ischemia, myocardial regeneration, antiangiogenesis in targeted tumor therapy |
| Diagnostic ultrasound–induced inertial cavitation | Commercially available | Intermittent diagnostic high-MI impulses | Improved downstream skeletal muscle perfusion in ischemic limbs (sickle-cell disease)<br>Improved microvascular outcome in acute coronary syndromes |

Porter TR, Mulvagh SL et al. J Am Soc Echocardiogr 2018 31, 241-274