Contrast other than myocardial perfusion

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Agenda

1. Contrast agents
2. Preparation for contrast echo
3. Clinical use of contrast echo
4. Pitfalls of contrast echo
5. Safety of contrast agent

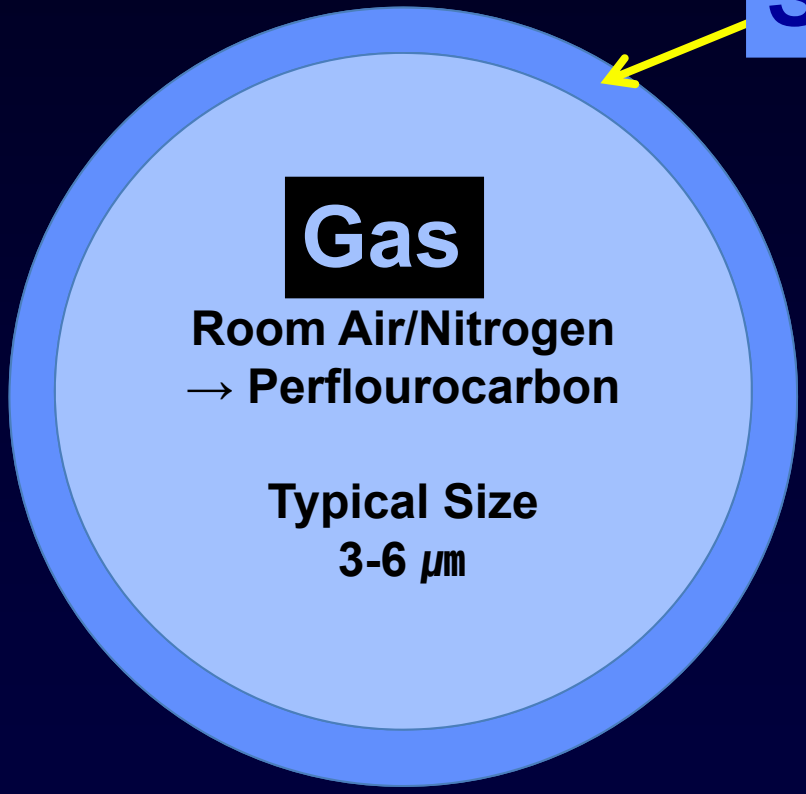
Use of contrast agents in clinical echocardiography

- First used in the mid-1970s ; agitated saline or agitated saline stabilized with indocyanine green dye -->did not transverse pulmonary circuit.
- Beginning in the early 1980s, a number of attempts for uniform in size, stability and homogenous and reproducible degree of contrast.

Ideal contrast microbubbles

- *Size less than 6 microns*
- *Uniform bubbles size*
- *Non-toxic*
- *Persistence of sufficient period*

Contents of a microbubble



- Rigidity
- Initial Size
- Surface Properties
- Ionic Charge
- Potential for Disruption
- Incorporated Biologicals

Determinants of microbubbles persistence

$$T = \frac{R^2 \times \rho}{2D \times Cs}$$

T= persistence

R=radius of bubbles

ρ =density of gas

D= diffusivity of gas

Cs=Concentration of saturation

Micrbubbles made of room air

- *Filtration by pulmonary capillaries*
- *Diffusivity of air*
- *Susceptibility to ambient LV pressure*

Micrbubbles made of fluorocarbons

- *Dense gases*
- *Low diffusivity*
- *Low saturation constant*

The evolution of contrast agents

Generation	Formulation	Characteristics
0	Free gas bubbles	Could not transverse pulmonary capillary
1	Encapsulated air bubbles	Successful trans-pulmonary passage
2	Encapsulated low solubility gas bubbles	Improved stability
3	Particulate gas bubbles	Controlled acoustic properties

Contrast agents for ultrasound

Agent	Bubble size (μm)	Gas	Shell composition	Indication
Levovist	2.0-3.0 (2.0-8.0)	Air	Lipid (palmitic acid)	LVO and Doppler
Optison*	4.7 (1.0-10.0)	Perfluoropropane	Human albumin	LVO, EBD, and Doppler
Definity*	1.5 (1.0-10.0)	Perfluoropropane	Phospholipid	LVO, EBD, and Doppler
Sonovue	2.5 (1.0-10.0)	Sulfar hexafluoride	Phospholipid	LVO, and Doppler
CARDIO sphere	4.0 (3.0-5.0)	Nitrogen	Biodegradable polymer bilayer	MCE
Imagify	2.0	Decafluorobutane	Synthetic polymer	LVO and MCE

* Approved by the FDA

J Am Soc Echocardiogr 2008;21

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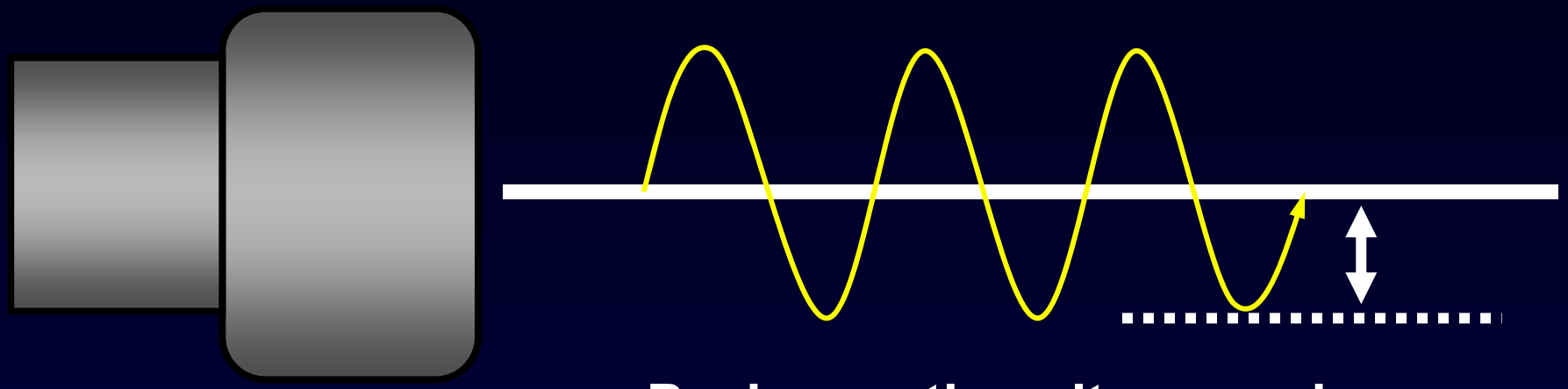
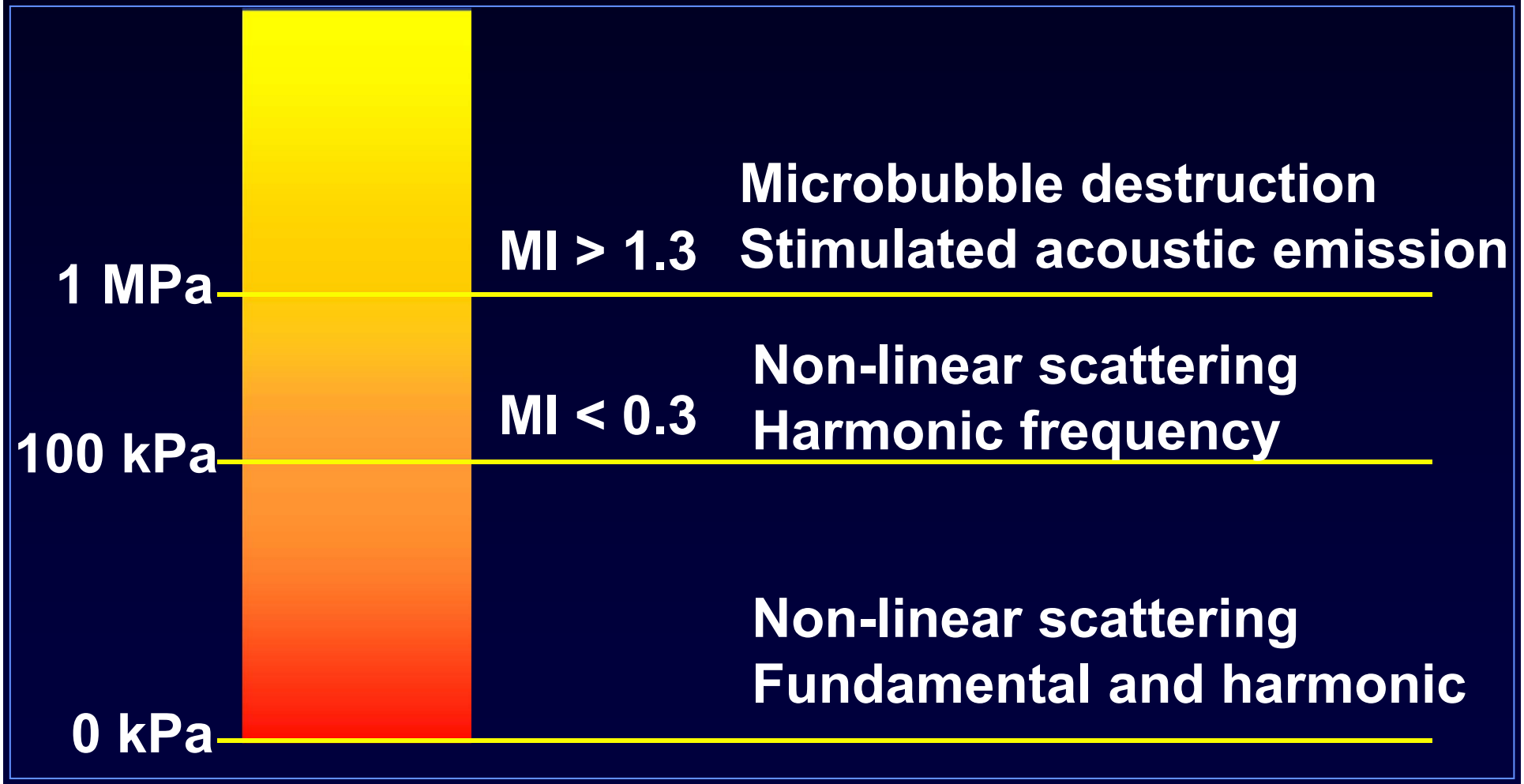
The Mechanical Index



Peak negative ultrasound pressure

$$\frac{\text{Peak negative ultrasound pressure}}{\sqrt{\text{Ultrasound frequency}}}$$

Effect of acoustic energy on μbubbles scattering properties



Initial settings for all system

- Imaging mode:

  harmonic B-mode and pulse inversion
- Dynamic range: low-medium
- Compression: medium-high
- Transmit power: MI <0.3

Individual adjustment

- Transmit power:
  reduction if apical defect or swirling
- Focus: below MV (apical planes)
  posterior wall (parasternal view)
- Receive gain:
  slightly reduce to decrease grey level in the myocardium before injection
- Time gain: as for non-contrast studies

Guidelines for injection

- IV start: 20G or larger
- Rate of bolus injection: 0.5~1 mL/s
- Slow saline flushing

  : 2~3 ml over 3~5 seconds
- When contrast is seen in RV, stop flush
- Administer additional IV dose as required

J Am Soc Echocardiogr 2008;11

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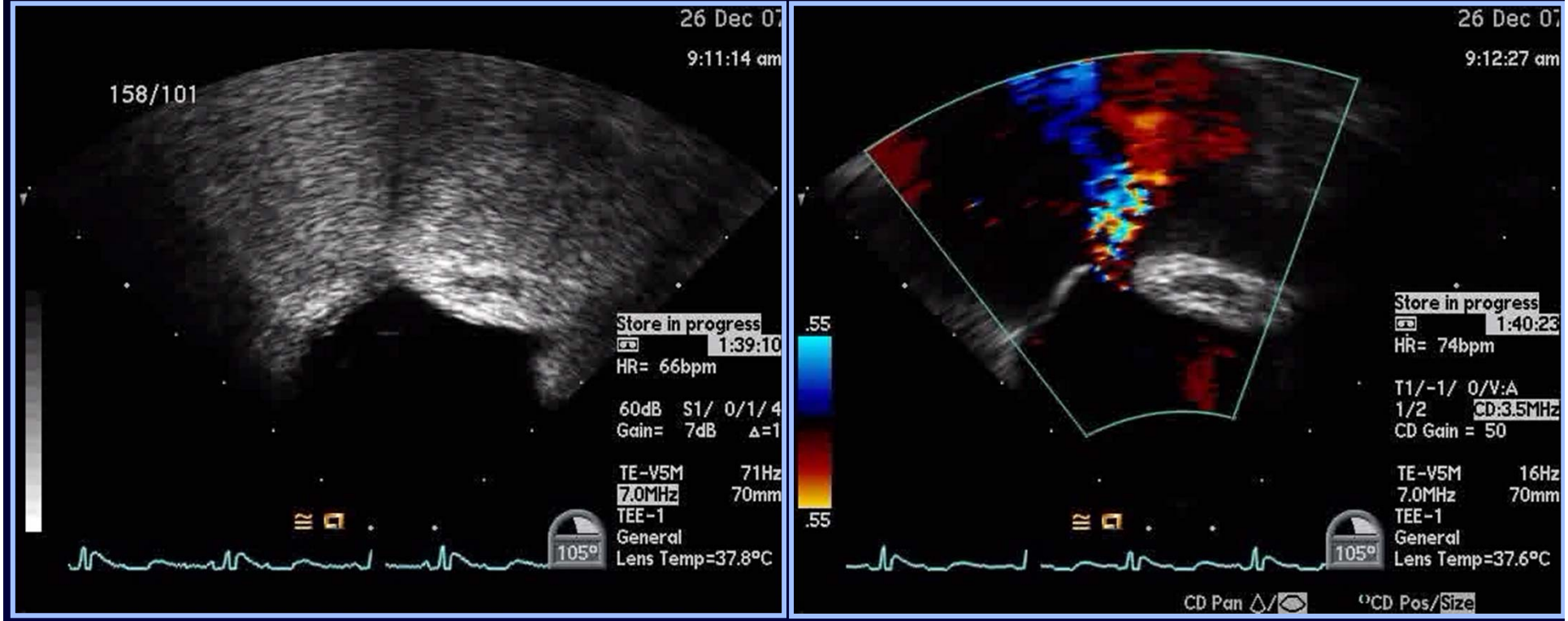
Clinical use of contrast echocardiography

- Detection of intracardiac shunt
- LV opacification for chamber delineation
- Refined definition of LV structural abnormalities
- Enhancement of Doppler signals
- Myocardial perfusion

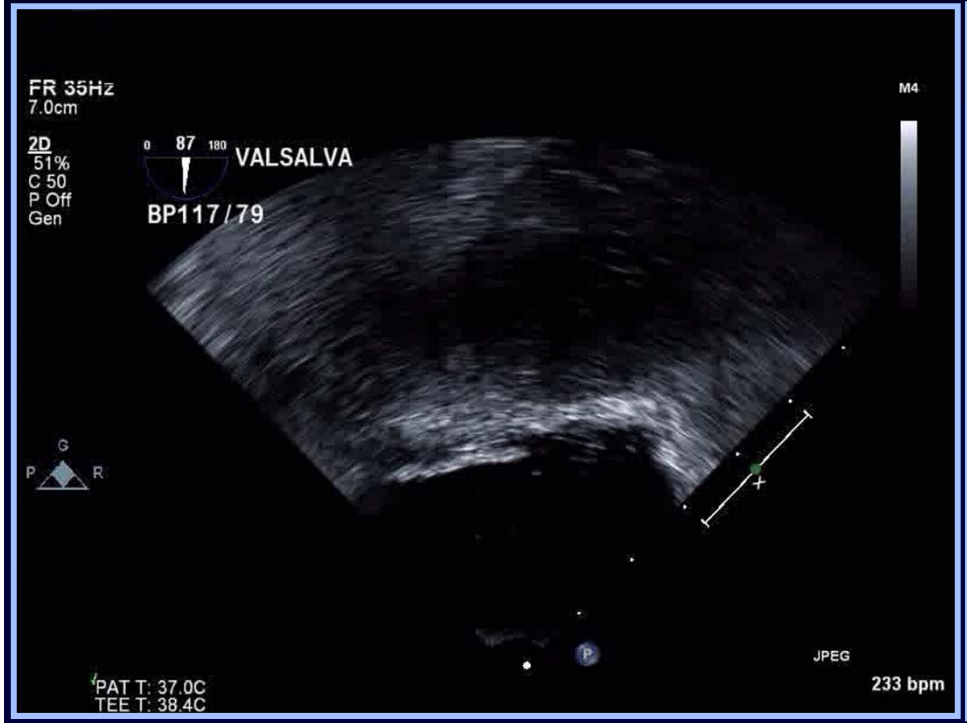
Intracardiac shunt detection

ASD



Intracardiac shunt detection

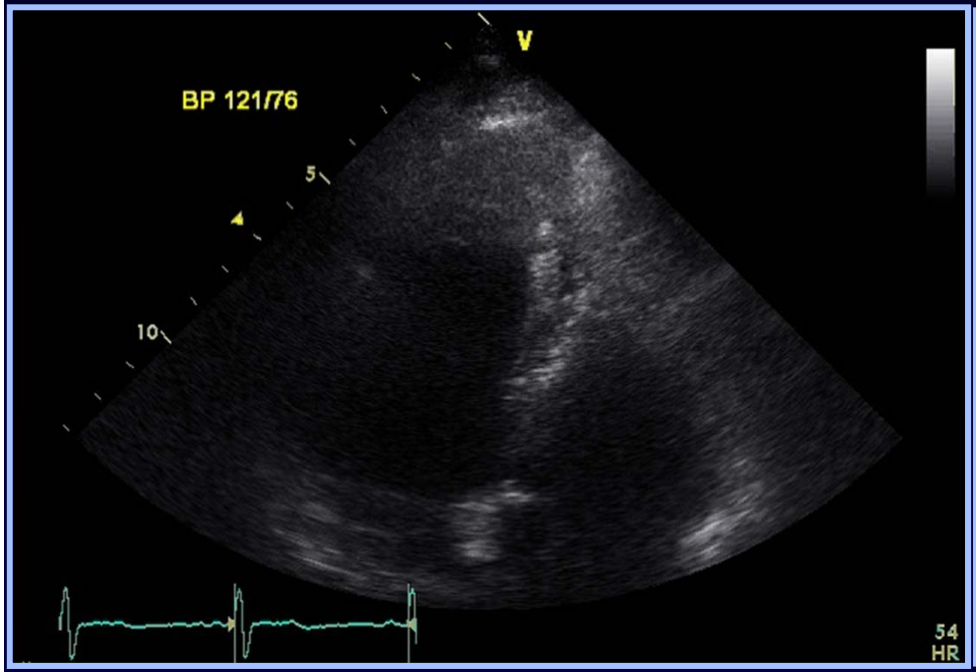
PFO

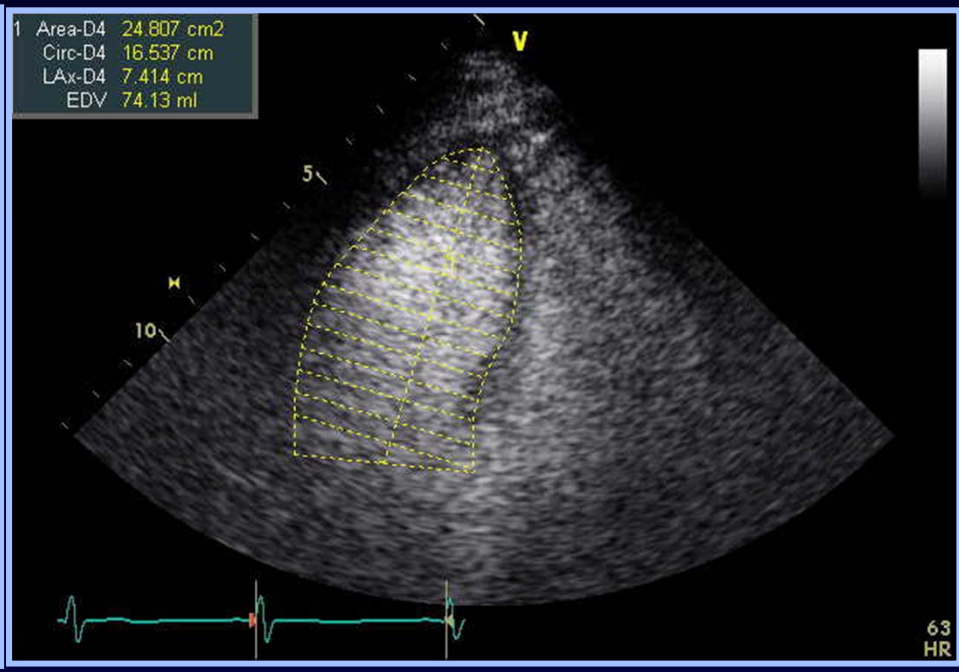


Intrapulmonary shunt

Measurement of LV volume and LV EF

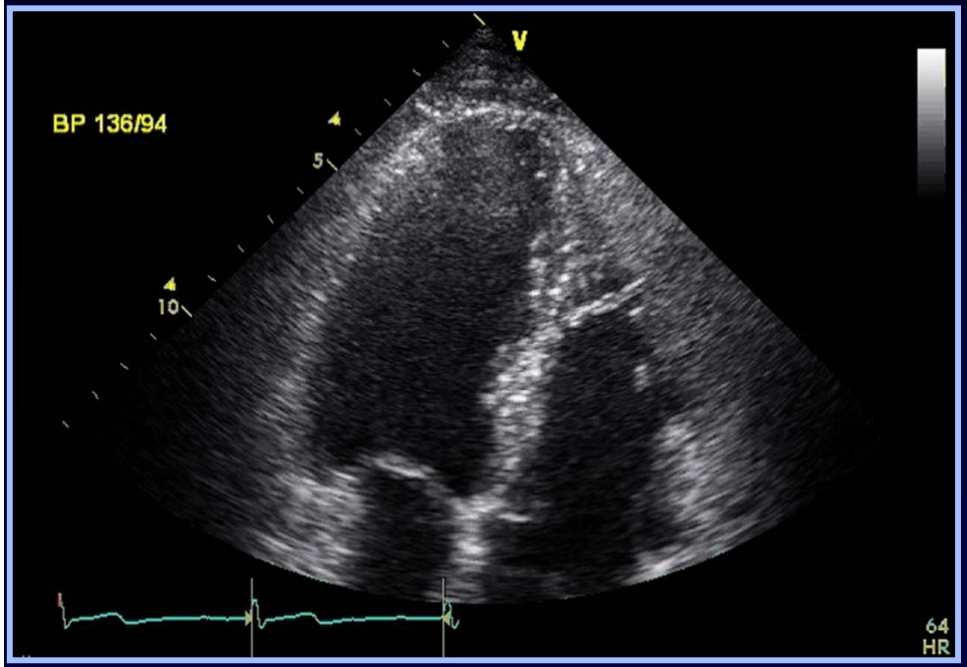
Anterior MI, poor echo window





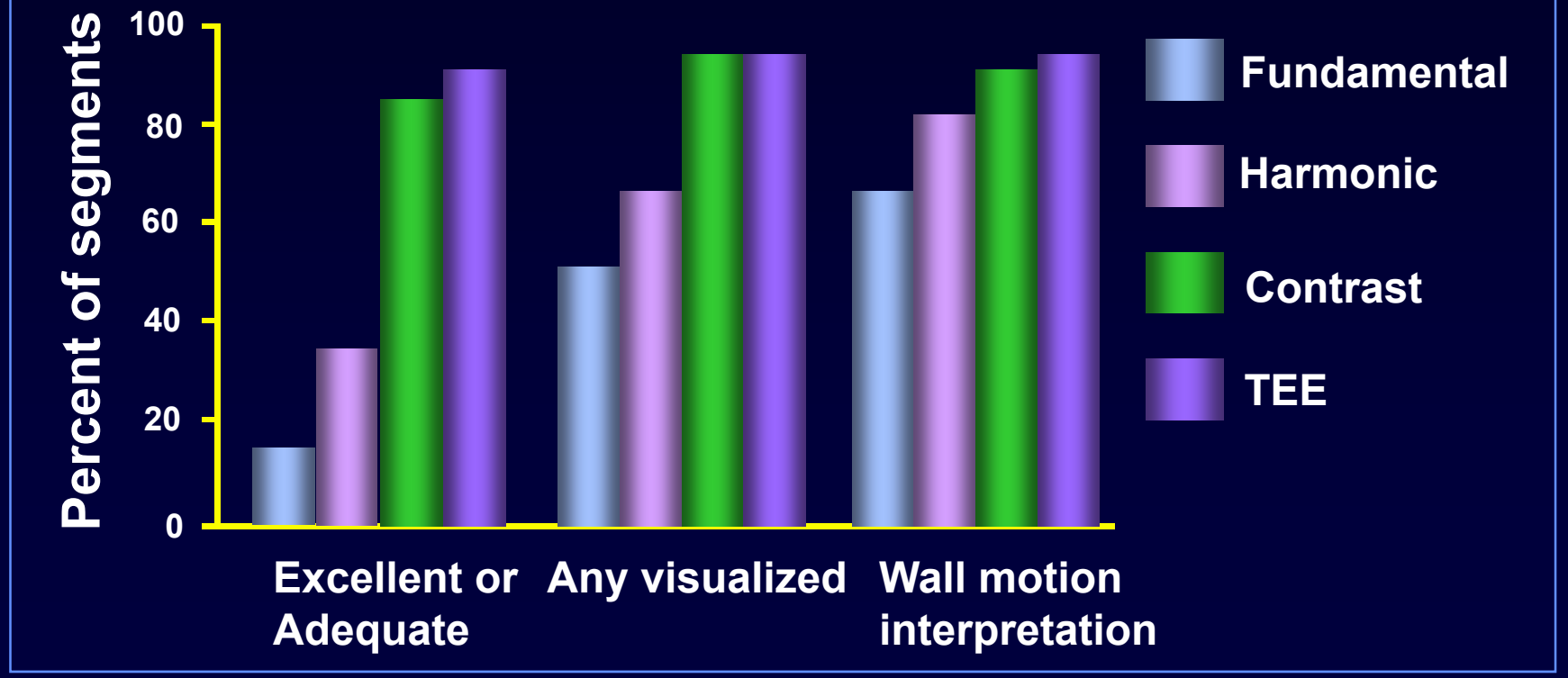
LV opacification for chamber delineation

Atypical chest pain



Diagnostic Accuracy and Cost-Effectiveness of Contrast Echocardiography on Evaluation of Cardiac Function in Technically Very Difficult Patients in the Intensive Care Unit

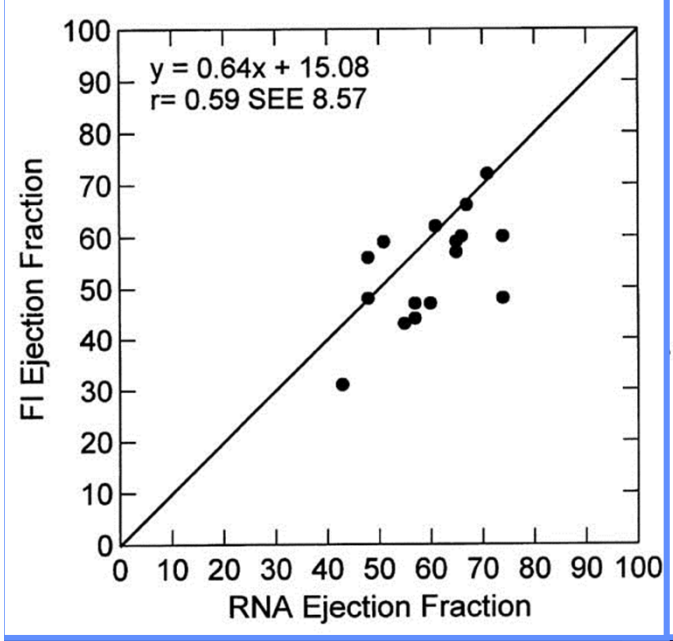
Yongqi Yong, MD, PhD, David Wu, MD, Valerian Fernandes, MD, Helen A. Kopelen, RDMS, Sarah Shimoni, MD, Sherif F. Nagueh, MD, Janice D. Callahan, PhD, Denise E. Bruns, MBA, Leslee J. Shaw, PhD, Miguel A. Quinones, MD, and William A. Zoghbi, MD

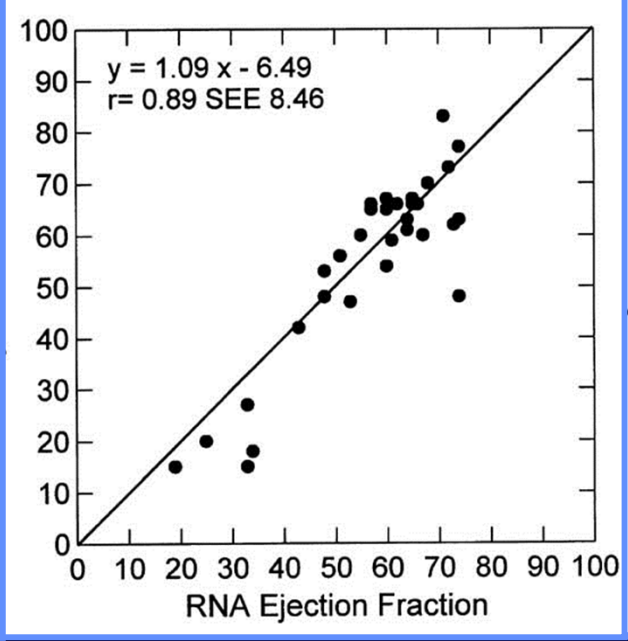


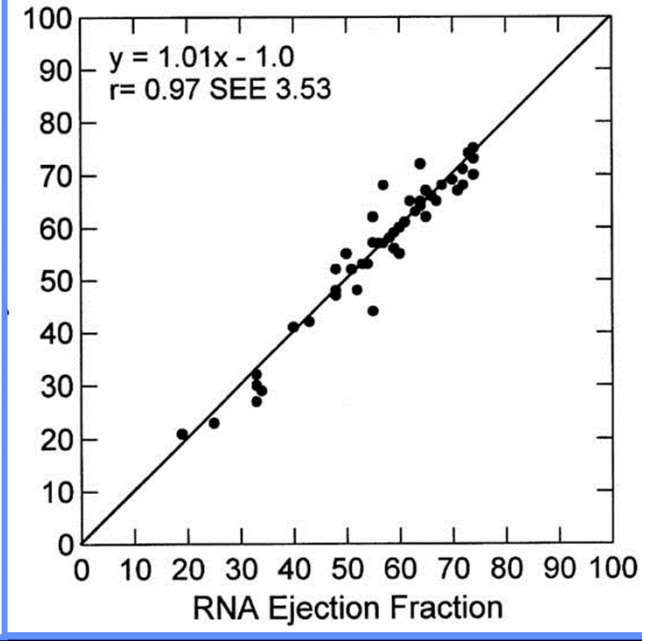
Am J Cardiol 2002;89:711–718

Feasibility and Accuracy of Left Ventricular Volumes and Ejection Fraction Determination by Fundamental, Tissue Harmonic, and Intravenous Contrast Imaging in Difficult-to-Image Patients

Fundamental	Harmonic	Contrast







J Am Soc Echocardiogr 2000;13

Incremental accuracy of contrast echo in the determination of LV volumes and LVEF

Study	Patients (n)	Gold-standard test	Echocardiographic parameter	Accuracy measured by linear correlation and corresponding SEE: UEE r	UEE SEE	UEE Gold standard, mean ± SD*	CEE r	CEE SEE	CEE Gold standard, mean ± SD*
Hundley et al (1998)[37]	35	MRI	LVEF	0.85	9%	−8 ± 6%	0.93	6%	+5 ± 3%
			LVEDV	0.92	21 mL	−21 ± 13 mL	0.95	15 mL	+15 ± 14 mL
			LVESV	0.94	25 mL	+17 ± 13 mL	0.97	20 mL	+12 ± 9 mL
Yu et al (2000)[33]	51	RNV	LVEF	0.59,† 0.89‡	8.6%,† 8.5%‡	−6 ± 9%,† −1 ± 8%‡	0.97	3.5%	−0.3 ± 4%
			LVEDV	0.61,† 0.71‡	22.8 mL,† 31.8 mL‡	−28 ± 65 mL,† −38 ± 82 mL‡	0.93	18.6 mL	−10 ± 40 mL
			LVESV	0.83,† 0.89‡	12.0 mL,† 23.5 mL‡	−5 ± 30 mL,† −10 ± 54 mL‡	0.97	10.0 mL	−2 ± 17 mL
Dias et al (2001)[36]	62	RNV	LVEF	0.76,† 0.74‡	7.6%,† 7.3%‡	−4 ± 8%,† −1 ± 7%‡	0.82	6.1%	−3 ± 6%
Hoffmann et al (2005)[38]	120	MRI, Cine V	LVEF	0.60,§ 0.72‖	NR	+0.8 ± 11%,§ −5.3 ± 13%‖	0.77,§ 0.83‖	NR	+4.6 ± 8.7%,§ −2.1 ±10.3%‖
			LVEDV	NR	NR	−72 ± 40 mL,§ −72 ± 84 mL‖	NR	NR	−42 ± 37 mL,§ −40 ± 37 mL‖
			LVESV	NR	NR	−36 ± 33 mL,§ −29 ± 51 mL‖	NR	NR	+27 ± 27 mL,§ −16 ± 53 mL‖

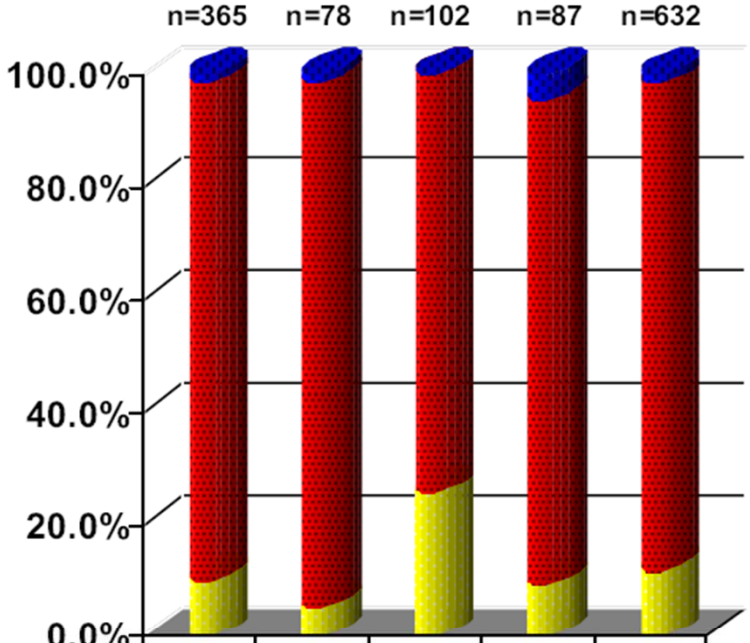
J Am Soc Echocardiogr 2008;11

Impact of Contrast Echocardiography on Evaluation of Ventricular Function and Clinical Management in a Large Prospective Cohort

Mustafa Kurt, MD, Kamran A. Shaikh, MD, Leif Peterson, PHD, Karla M. Kurrelmeyer, MD, FACC, Gopi Shah, MD, FACC, Sherif F. Nagueh, MD, FACC, Robert Fromm, MD, Miguel A. Quinones, MD, FACC, William A. Zoghbi, MD, F
Houston, Texas

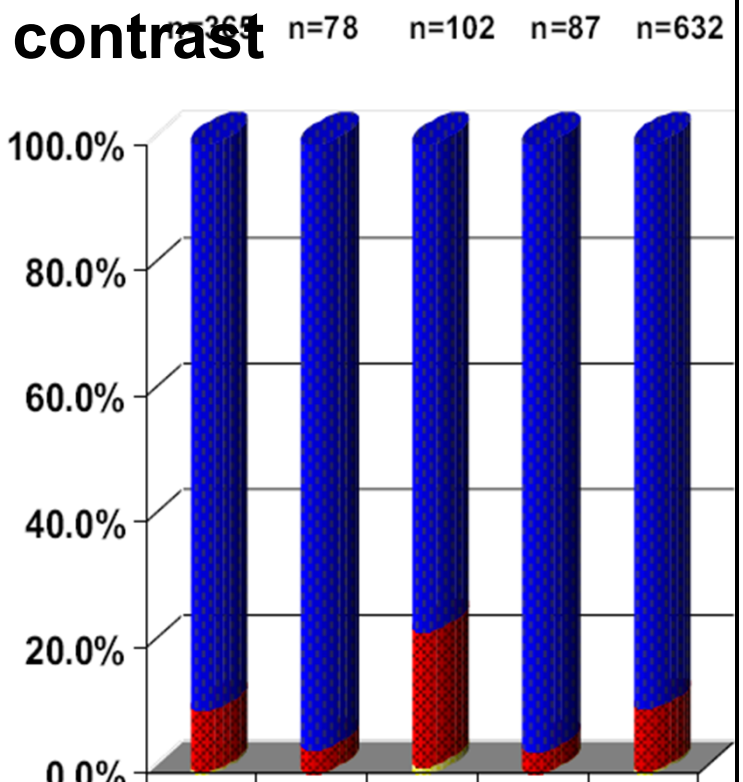
J Am Coll Cardiol 2009;53

Before contrast



	Inpt Wards	MICU	SICU	Out patient	Total
Adequate	1.4%	1.3%	0.0%	4.6%	1.6%
Technically Difficult	88.8%	93.6%	74.5%	86.2%	86.7%
Uninterpretable	9.9%	5.1%	25.5%	9.2%	11.7%

After contrast



	Inpt Wards	MICU	SICU	Out patient	Total
Adequate*	90.1%	96.2%	78.4%	96.6%	89.9%
Technically difficult*	9.6%	3.8%	21.6%	3.4%	9.8%
Uniterpretable*	0.3%	0.0%	1.0%	0.0%	0.3%

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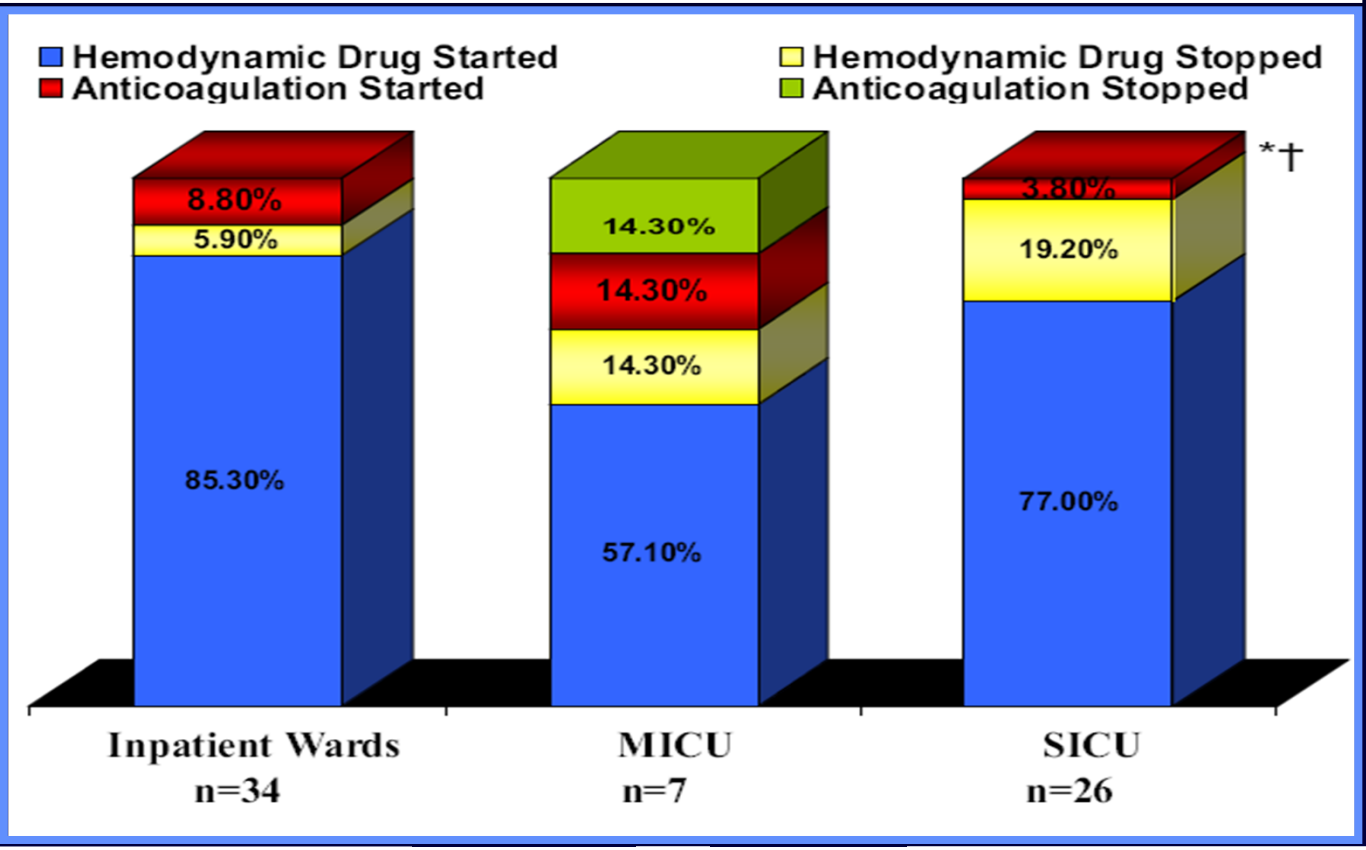
Houston, Texas

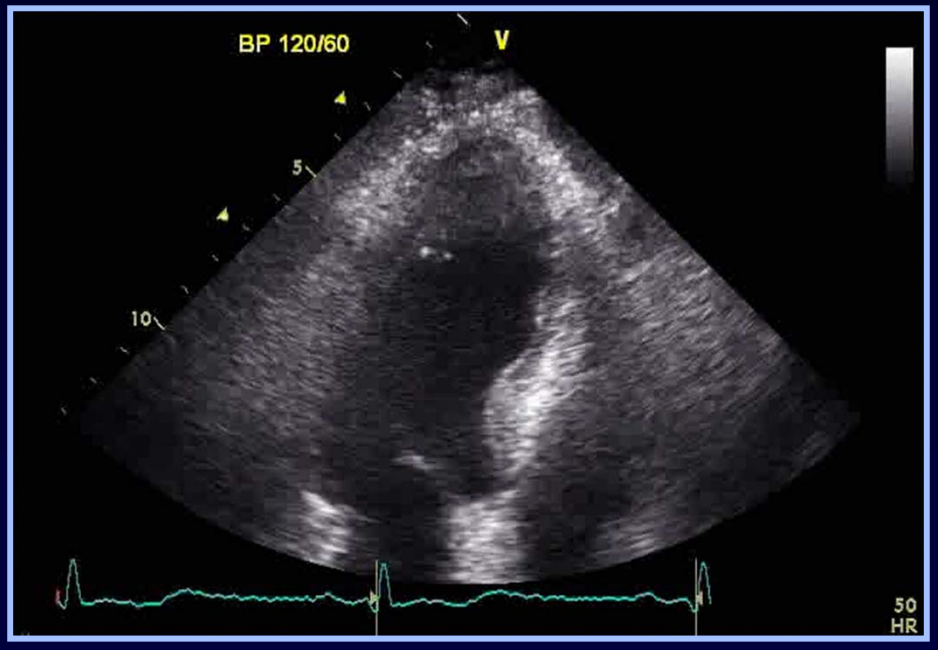
J Am Coll Cardiol 2009;53

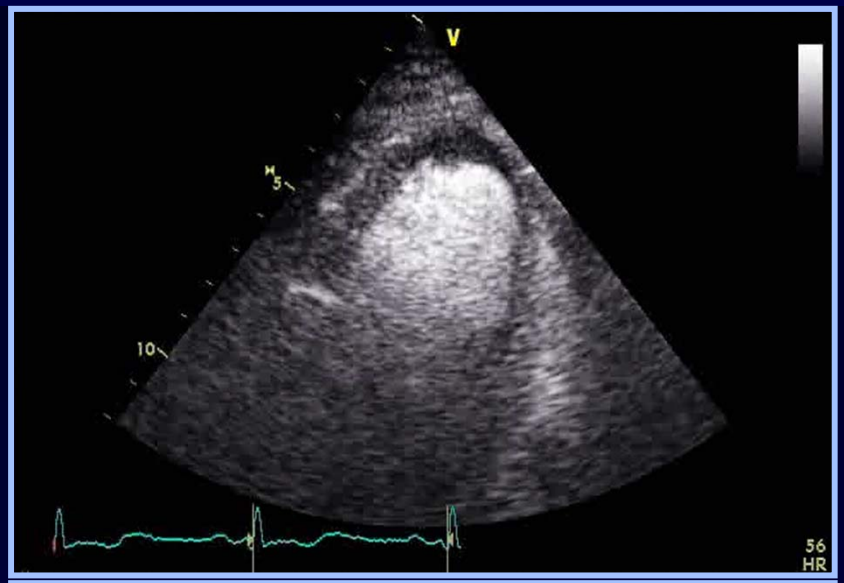
Impact of Contrast on Medication Changes

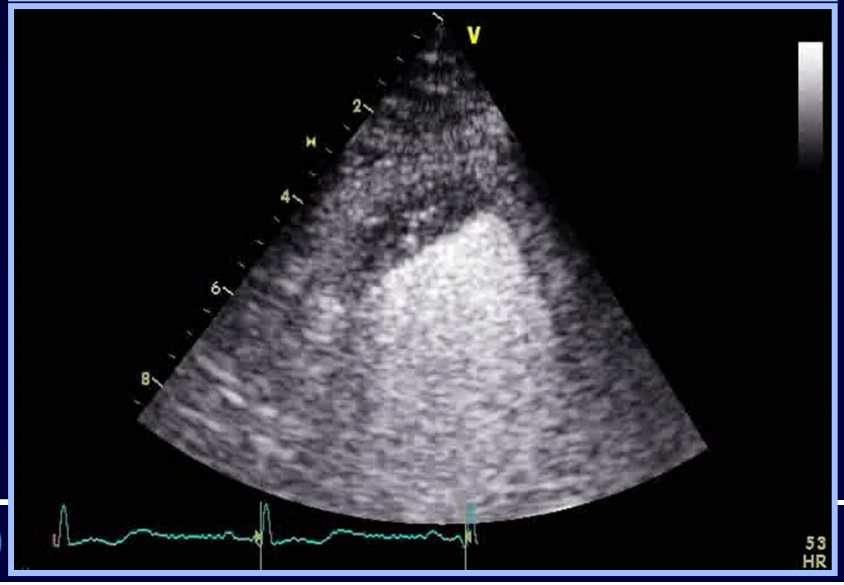


Refined definition of LV structural abnormalities

Apex mural thrombi

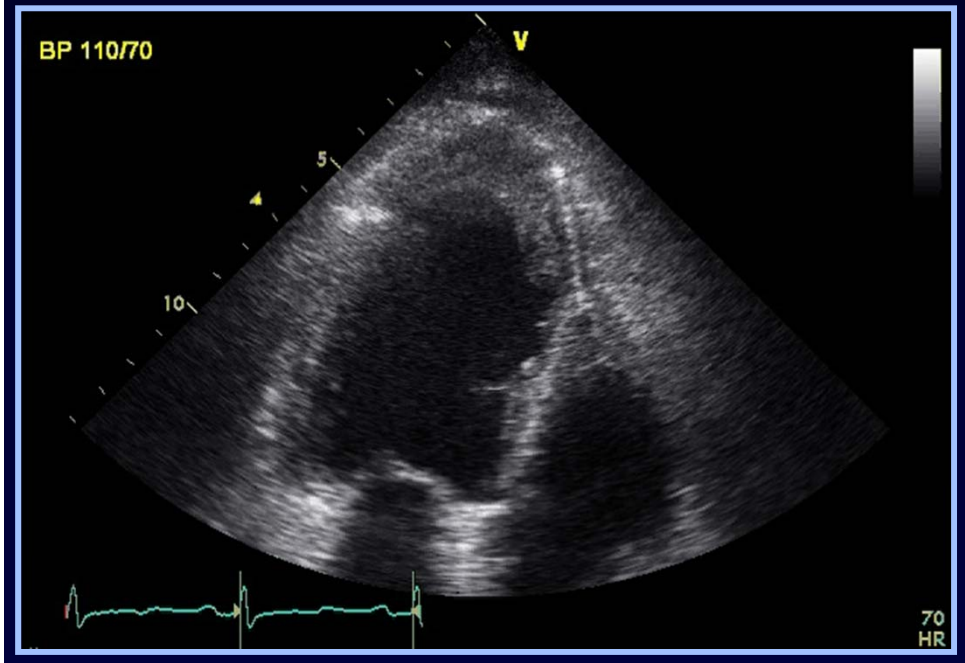


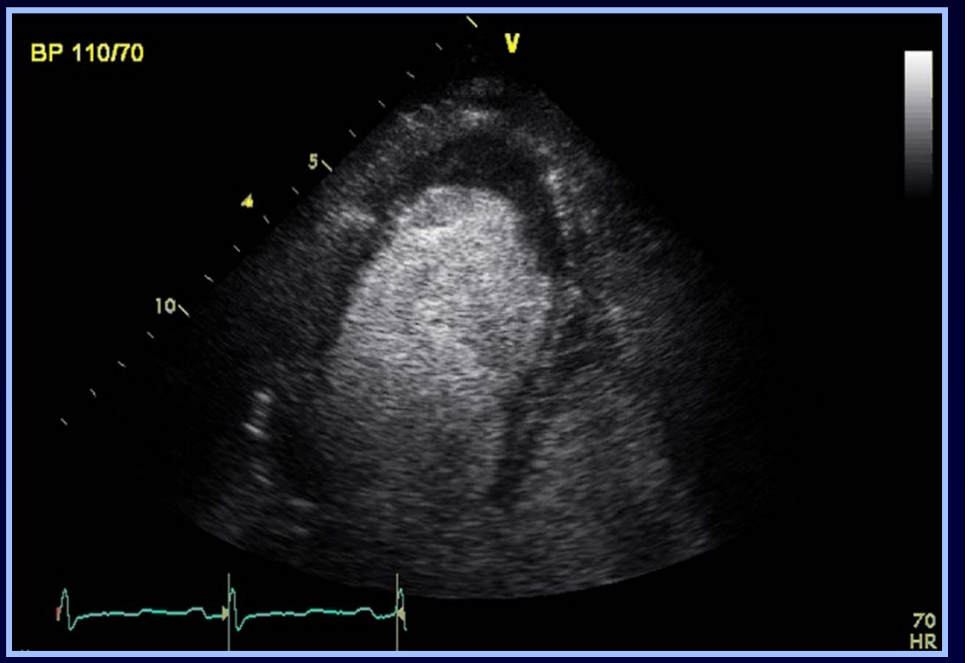




Refined definition of LV structural abnormalities

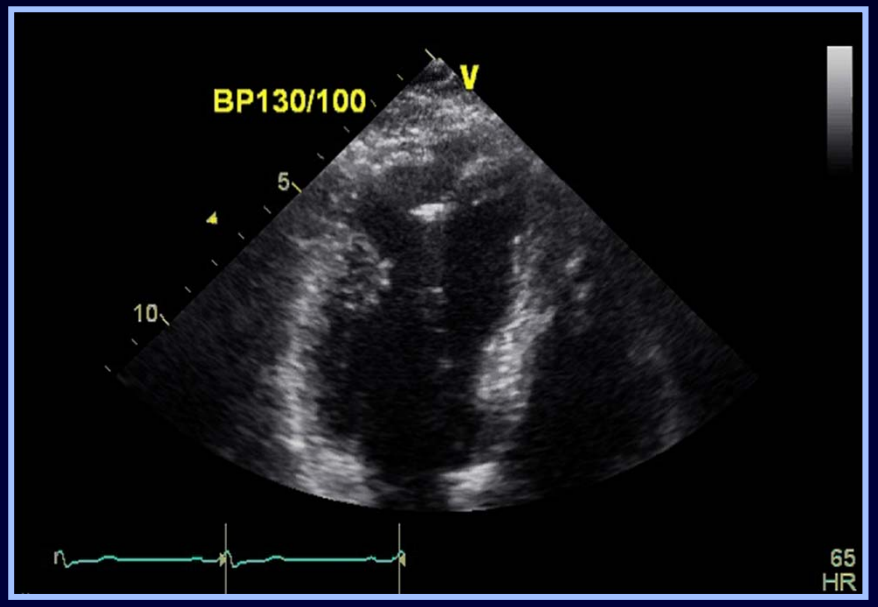
Hypereosionophilic SD

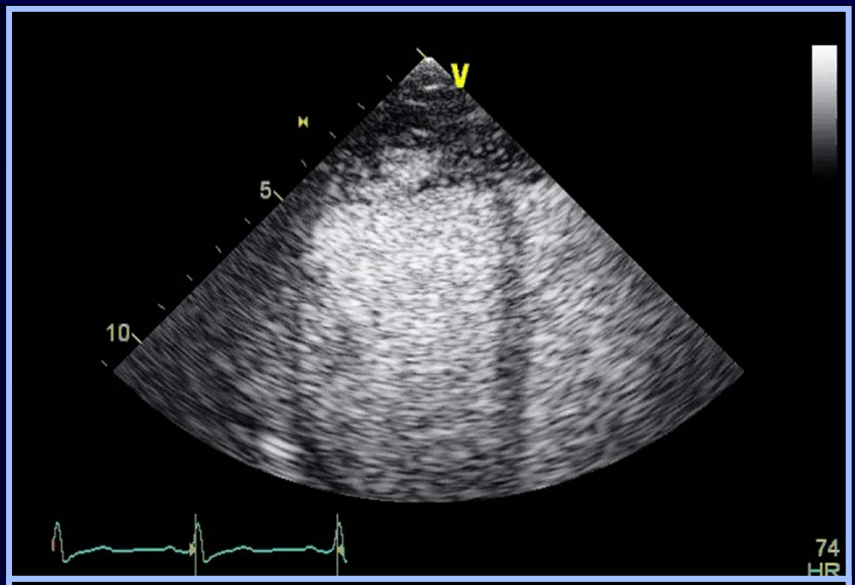


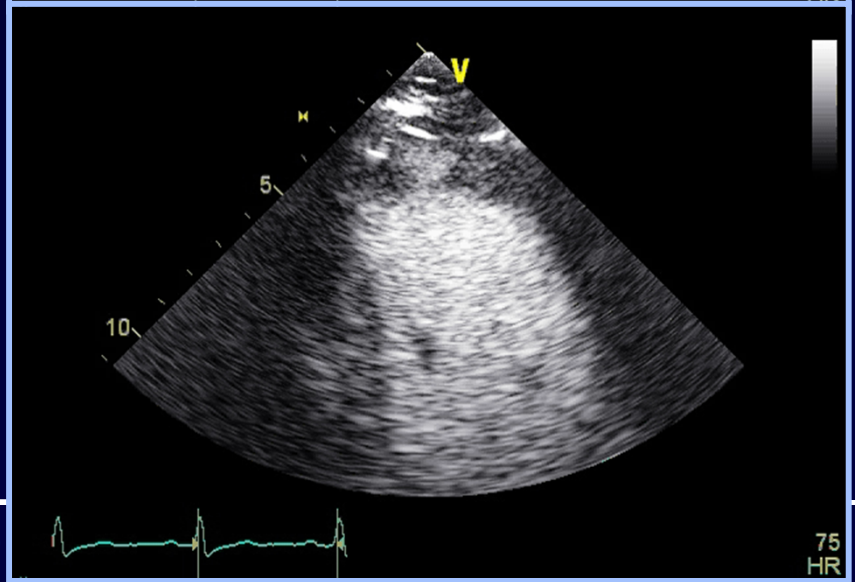


Refined definition of LV structural abnormalities

Apical aneurysm

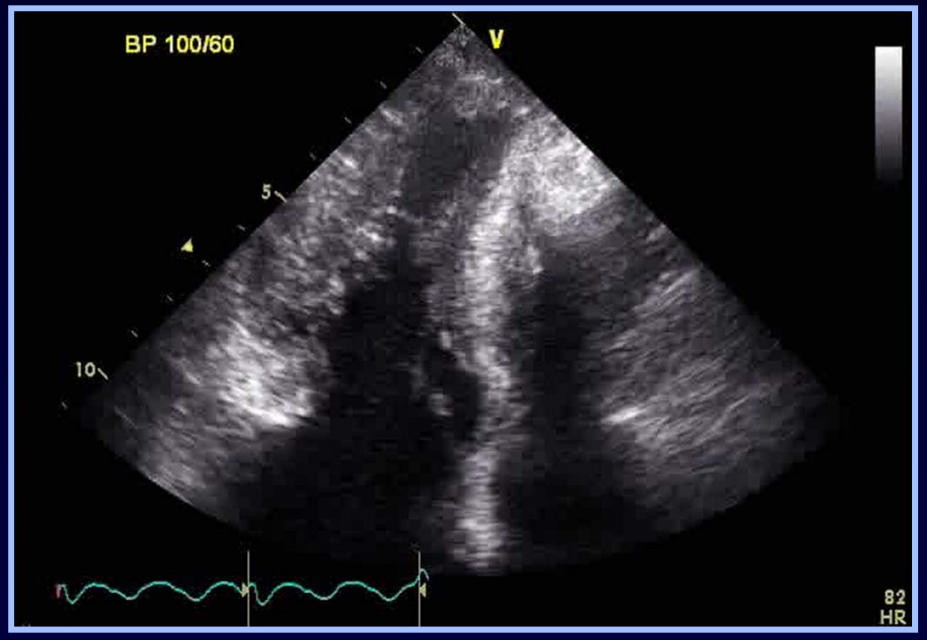


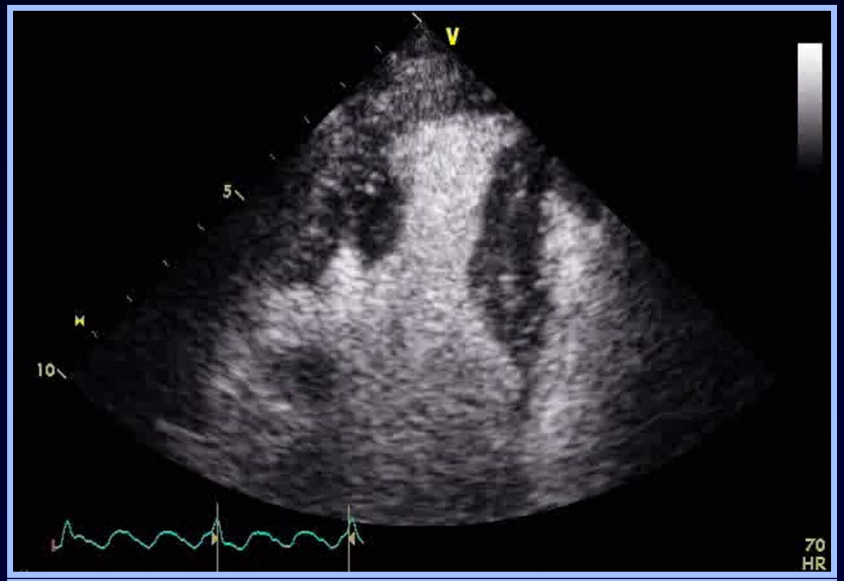


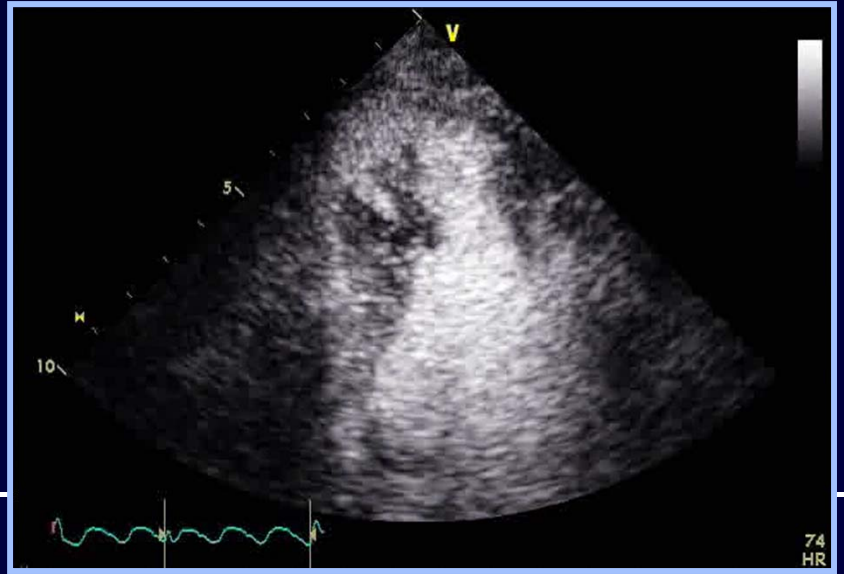


Refined definition of LV structural abnormalities

HCMP

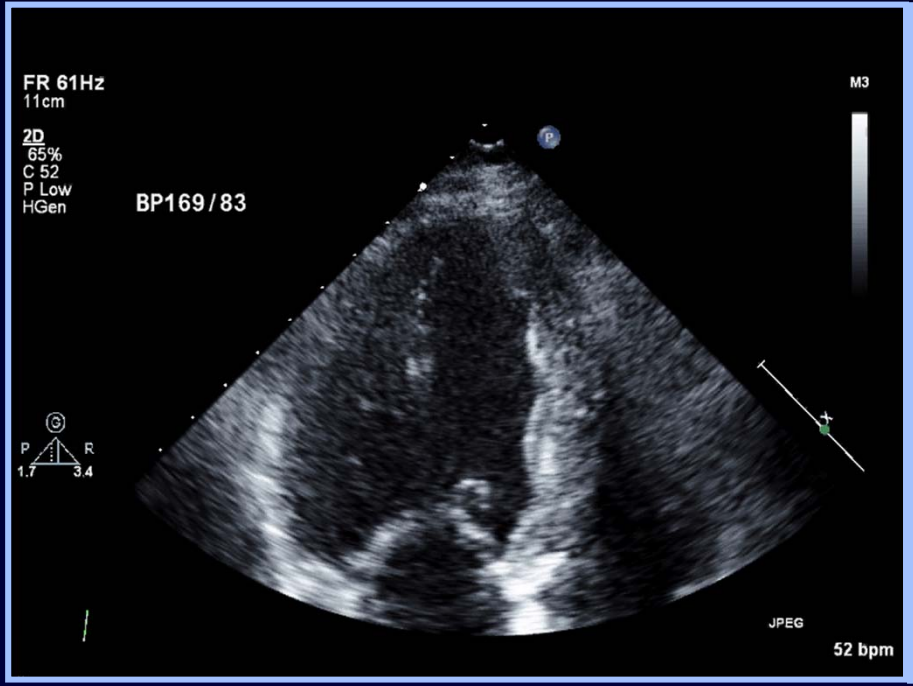


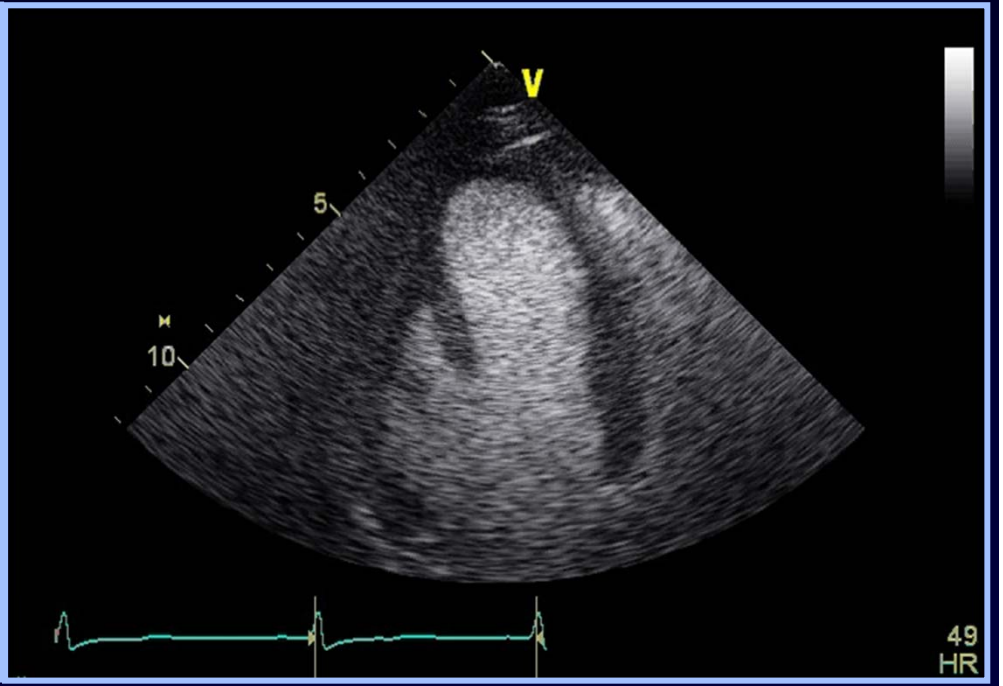




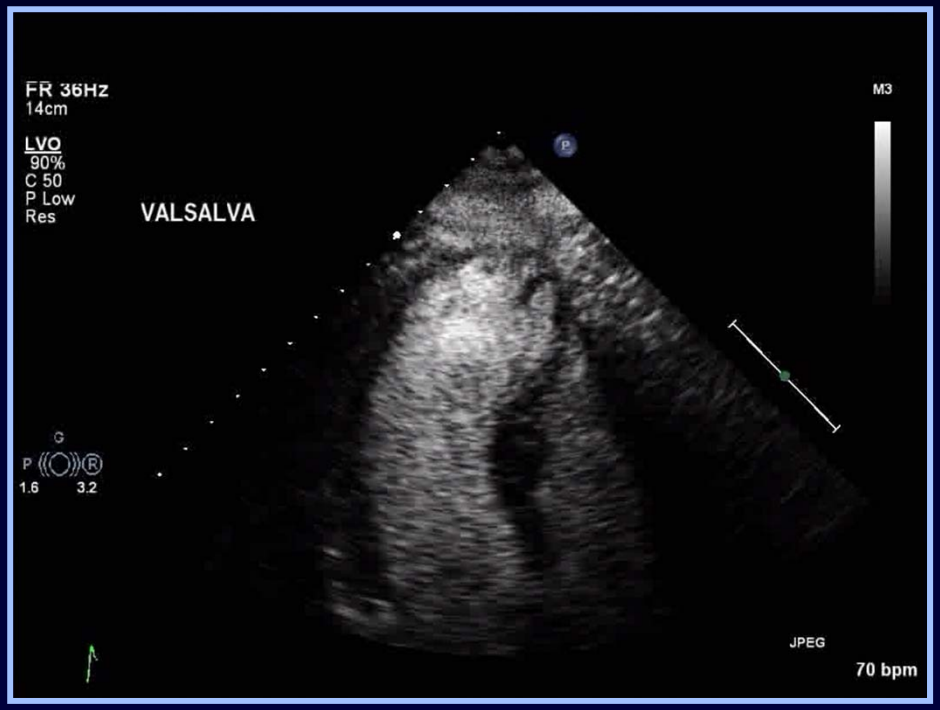
Refined definition of LV structural abnormalities

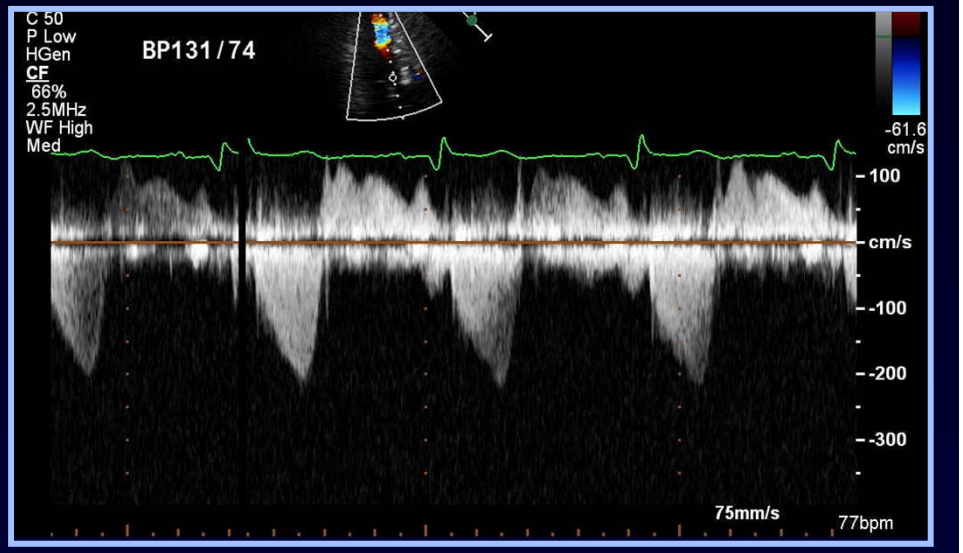
Accessory papillary muscle

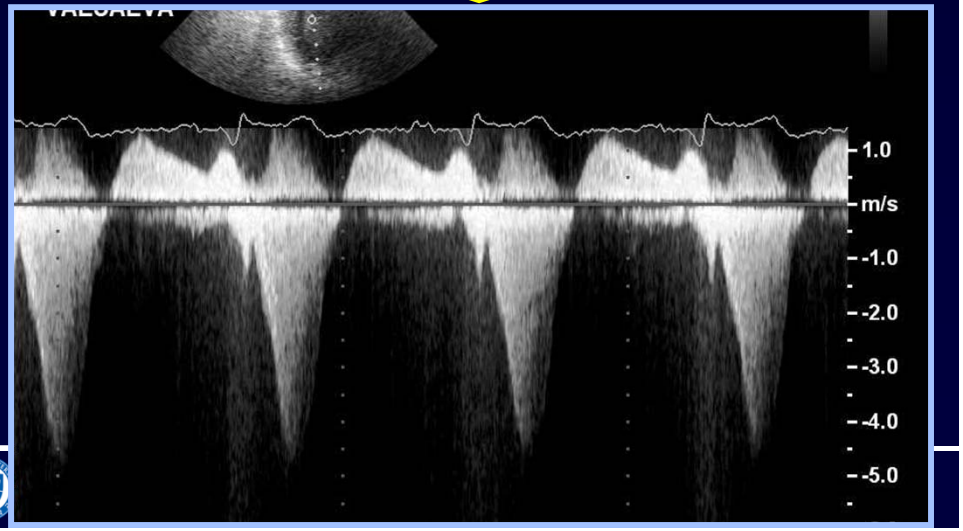




Enhancement of Doppler signals







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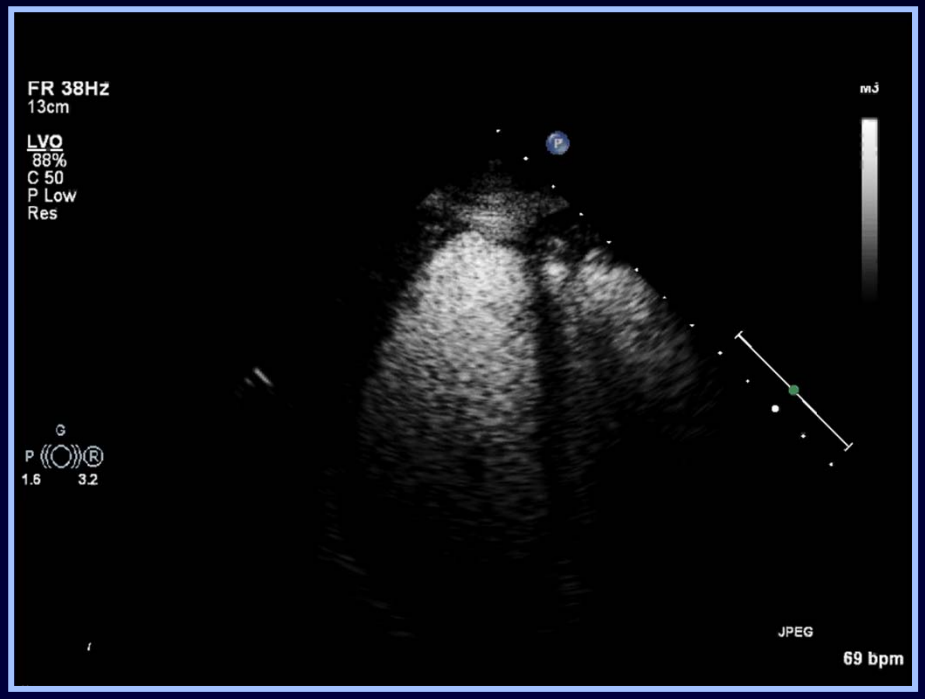
Contrast artifacts

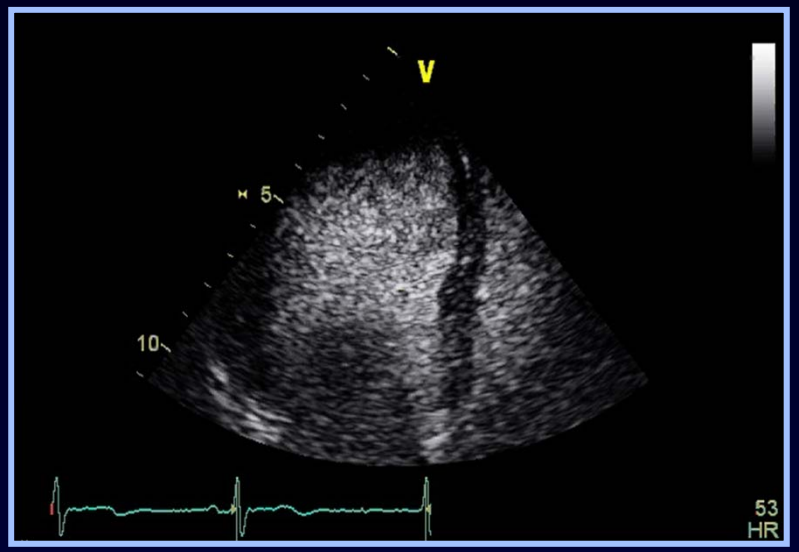
- *Attenuation*
- *Shadowing*
- *Microbubbles destruction*
- *Competitive flow*

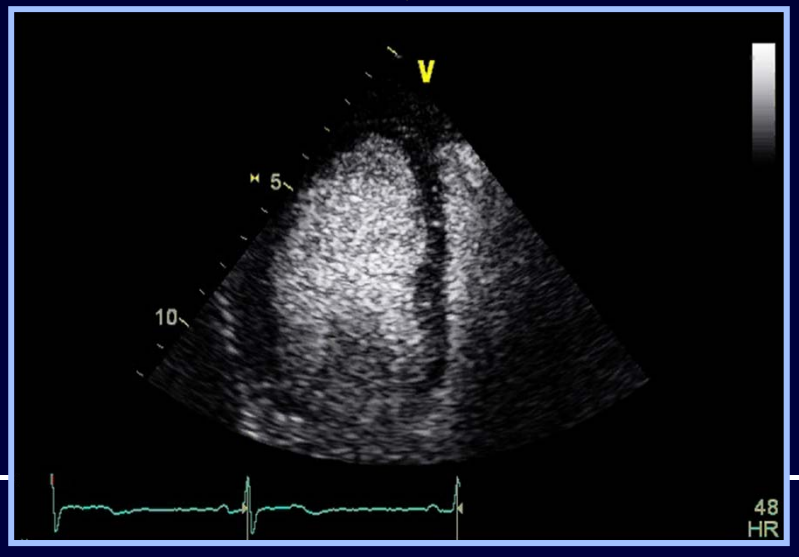
Contrast artifacts



- As contrast agents are very potent reflectors, their high concentration results in attenuation.
- Area behind that of high concentration can be shadowed.
- This can be avoided by delaying scanning after the peak contrast effect, or by lowering concentration.

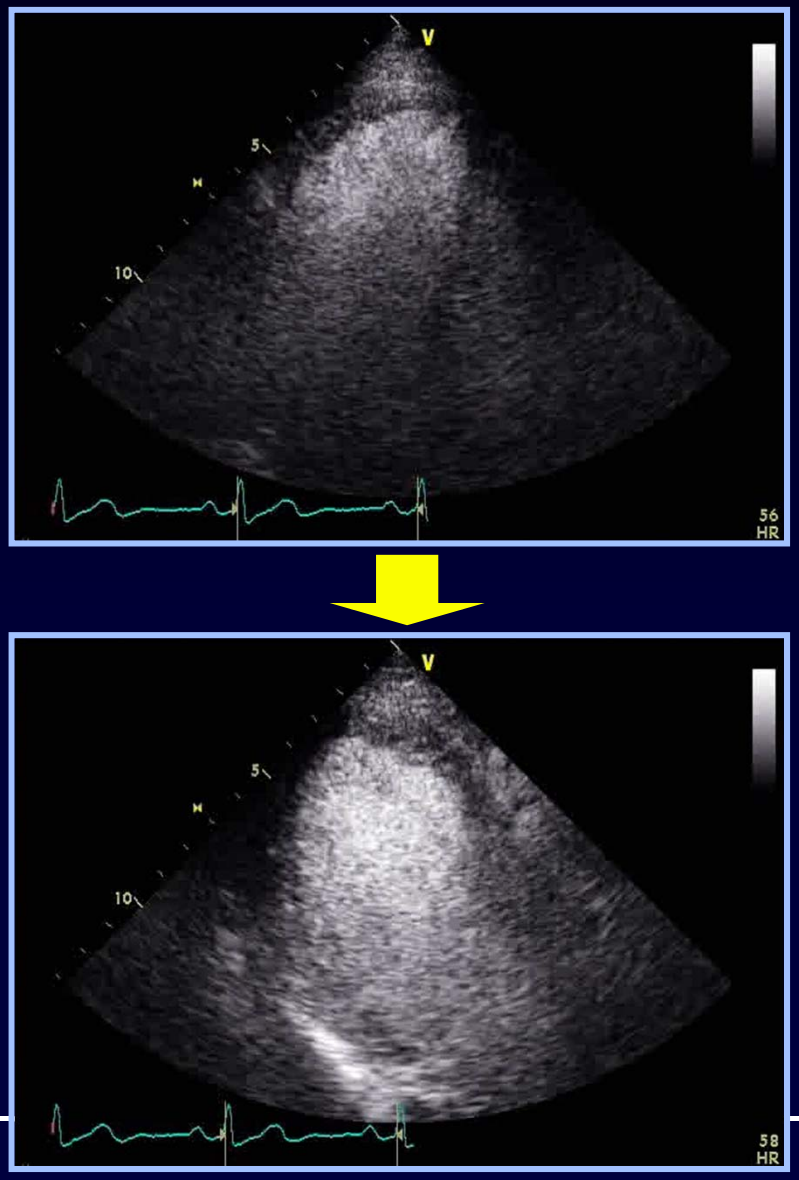
Contrast artifacts





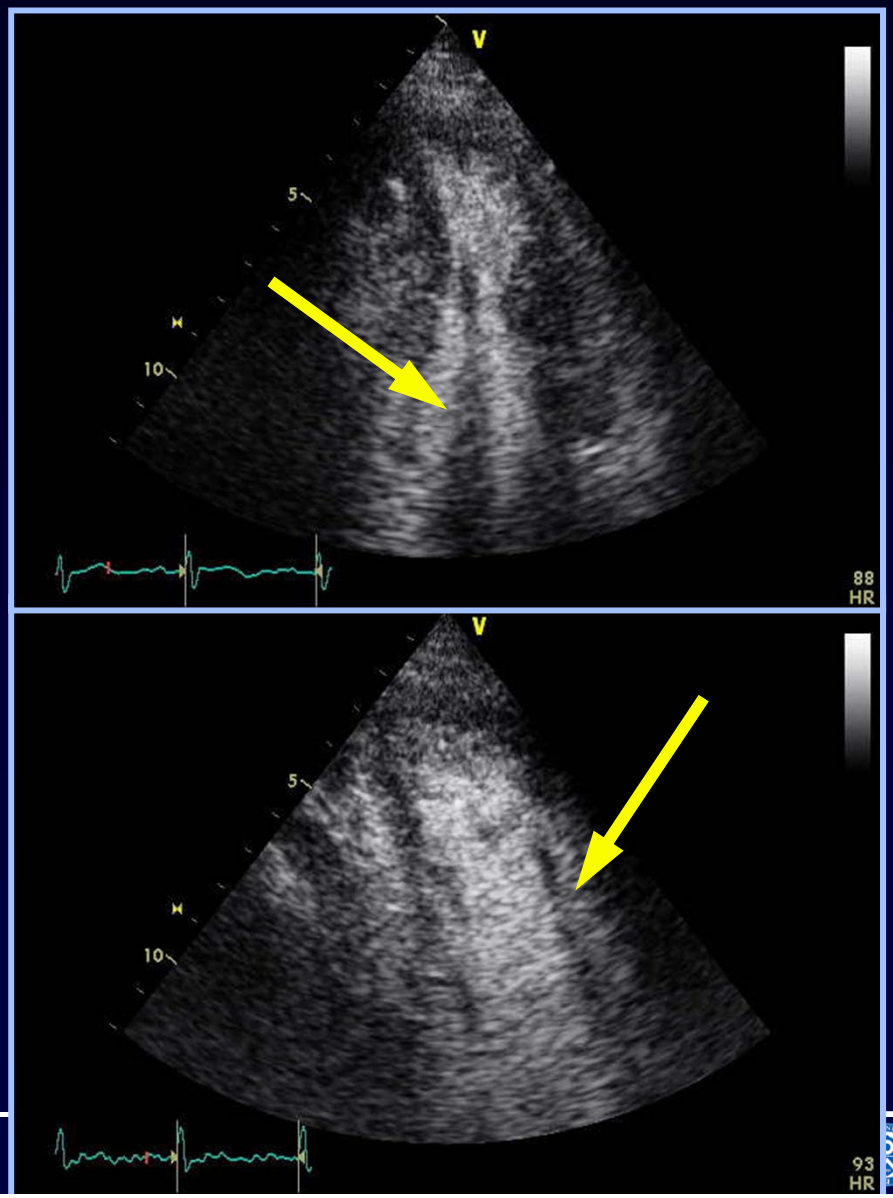
- The amount of microbubble destruction is directly related to the intensity of the ultrasound beam.
- At a high mechanical index, microbubbles are rapidly destroyed, predominantly in the near field.
- Can be solved by reducing the mechanical index <0.3

Contrast artifacts



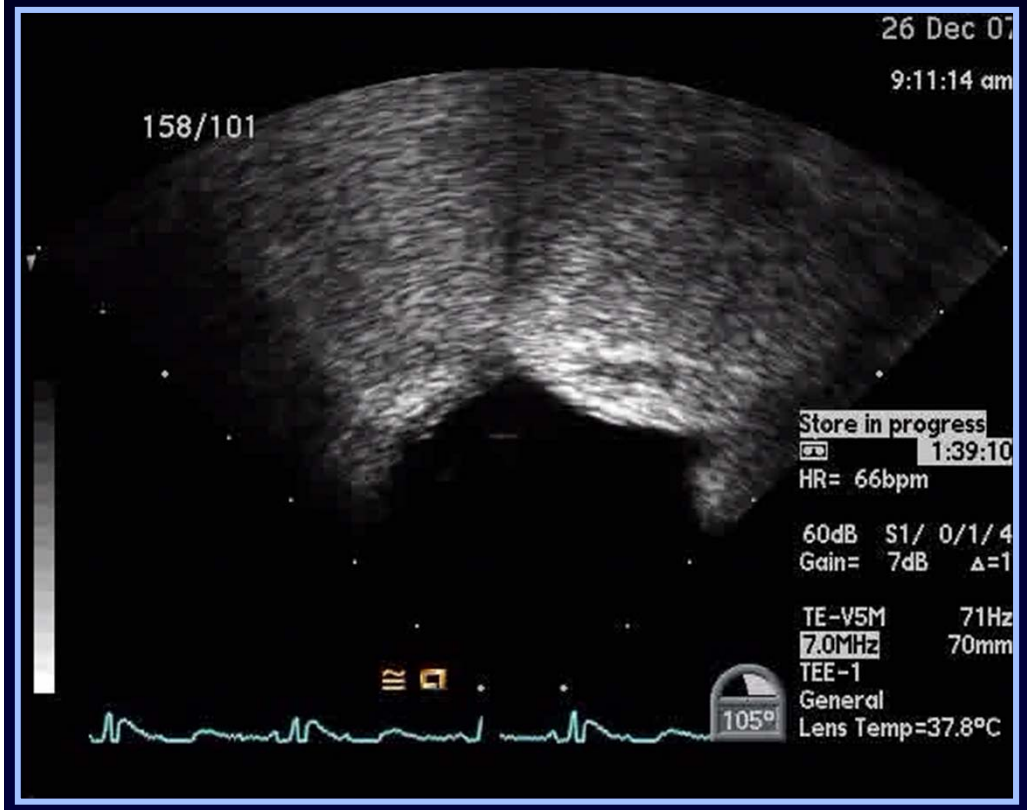
- If there is insufficient cavity contrast at all depth, increasing dose can be helpful.

Contrast artifacts



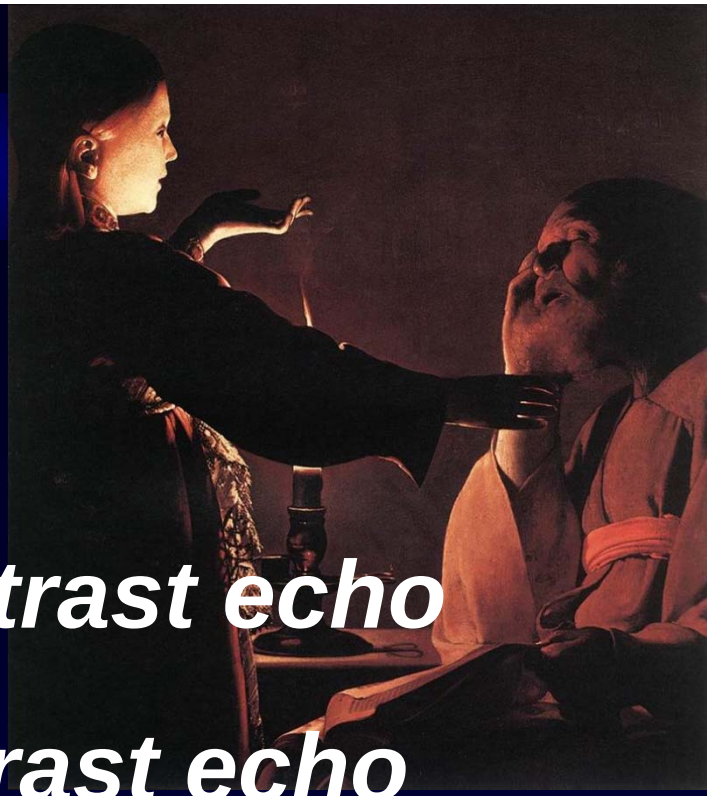
- Dense fibrosis, calcification or papillary muscle can make shadow.
- Shadowing from papillary muscle can be confused with the lateral endocardial border.

Contrast artifacts



- If there is competing flow from another vessel that is not contrast enhanced, a negative contrast effect will occur.
- This is often seen after intravenous injection of saline contrast for evaluating an ASD.

Agenda



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5. *Safety of contrast agent*

MedWatch The FDA Safety Information and Adverse Event Reporting Program

Safety Information

Safety Alerts for Human Medical Products

2010 Safety Alerts for Human Medical Products

2009 Safety Alerts for Human Medical Products

2008 Safety Alerts for Human Medical Products

2007 Safety Alerts for Human Medical Products

2006 Safety Alerts for Human Medical Products

2005 Safety Alerts for Human Medical Products

2004 Safety Alerts for Human Medical Products

Micro-bubble Contrast Agents (marketed as Definity (Perflutren Lipid Microsphere) Injectable Suspension and Optison (Perflutren Protein-Type A Microspheres for Injection) October 2007

Audience: Radiologists, radiology technicians, cardiologists, other healthcare professionals

[Posted 10/12/2007] FDA has received reports of deaths and serious cardiopulmonary reactions following the administration of ultrasound micro-bubble contrast agents used in echocardiography. Four of the 11 reported deaths were caused by cardiac arrest occurring either during infusion or within 30 minutes following the administration of the contrast agent; most of the serious but non-fatal reactions also occurred in this time frame. As a result, the manufacturers of Definity and Optison have agreed to revise the labeling for these products in order to optimize their safe use.

Revised labeling includes changes to the following sections: BOXED WARNING, CONTRAINDICATIONS, WARNINGS, and a statement in the INDICATIONS section cautioning that the safety and efficacy of the use of Definity with exercise or pharmacological stress testing have not been established. Together these labeling changes emphasize the risk for serious cardiopulmonary reactions, and that the use of these products is contraindicated in patients with unstable cardiopulmonary status, including patients with unstable angina, acute myocardial infarction, respiratory failure, or recent worsening congestive heart failure.

[October 12, 2007 - Drug Information Page - FDA]
[October 12, 2007 - Information for Healthcare Professionals - FDA]

Drug Safety and Availability

Postmarket Drug Safety Information for Patients and Providers

- Index to Drug-Specific Information
- Approved Risk Evaluation and Mitigation Strategies (REMS)
- Postmarketing Safety Evaluation of New Molecular Entities: Final Report
- Drug Safety Information for Healthcare Professionals

Micro-bubble Contrast Agents (marketed as Definity (Perflutren Lipid Microsphere) Injectable Suspension and Optison (Perflutren Protein-Type A Microspheres for Injection)

FDA ALERT [10/2007, updated 7/17/2008] - FDA is issuing this alert to update healthcare professionals about changes that were made to the *Boxed Warning, Warnings*, and *Contraindications* sections of the prescribing information for micro-bubble contrast agents in May and June, 2008. The revised *Boxed Warning* and *Warnings* continue to highlight the risk of serious cardiopulmonary reactions during or within 30 minutes following the administration of these products and recommend that high risk patients with pulmonary hypertension or unstable cardiopulmonary conditions be closely monitored during and for at least 30 minutes post administration of these contrast agents. Concurrent with these labeling changes, FDA required that manufacturers of micro-bubble contrast agents conduct clinical studies to more thoroughly assess the risks for serious cardiopulmonary reactions.

Several of the *Contraindications* that were added to the labeling in October, 2007 were removed because FDA determined that, in some patients, the benefits from the diagnostic information that could be obtained through the use of Definity or Optison may outweigh the risk for serious cardiopulmonary reactions, even among some patients at particularly high risk for these reactions. The *Contraindications* that were removed include: worsening or clinically unstable congestive heart failure, acute myocardial infarction or acute coronary syndromes, serious ventricular arrhythmias or high risk of arrhythmias due to prolongation of the QT interval, respiratory failure, severe emphysema, pulmonary emboli or other conditions that cause pulmonary hypertension.

These changes reflect conclusions of FDA reviews related to information received following the addition of new contraindications and warnings to the labeling for these products in October 2007.

Safety and Efficacy of Commercially Available Ultrasound Contrast Agents for Rest and Stress Echocardiography
A Multicenter Experience

- 42,408 consecutive patients from 1999 to 2007
  at 3 academic medical centers
  Saint Louis University
  University of Nebraska
  Mayo Clinic Rochester–Minnesota
- No significant differences in death rates or MIs between patients who did and did not receive contrast during their rest and stress echo.

J Am Coll Cardiol 2009;53

Rest Echocardiography

Among 23,659 patients

- no events within 30 min
- 3 nonfatal MIs and 1 death within 24 h

In the matched group of 5,900 patients

- no events within 30 min,
- 7 nonfatal MIs and 1 death within 24 h (p= NS)

Stress echocardiography

Among 18,749 patients

- no deaths or MIs within 30 min
- 1 death within 24 h
- 5 nonfatal MIs within 24 h; 3 Definity and 2 Optison

J Am Coll Cardiol 2009;53

Comparative mortality in selected cardiac procedures

Procedures	Mortality
Contrast Echo	1:145,000 (SonoVeu), 1:500,000 (Definity)
Myocardial Scintigraphy	1:10,000
Exercise ECG	1:2,500 (or AMI)
Coronary arteriography	1:1,000

Eur J Echocardiogr 2009;10

Take home message

- With development of contrast agents and imaging modalities, contrast echocardiography significantly improves the image quality.
- Contrast echocardiography allows assessment of cardiac anatomy, function and perfusion in optimal technical settings.
- Safety concerns need to be evaluated, but the benefits from the diagnostic information should be considered.


Thank you for
your attention!!