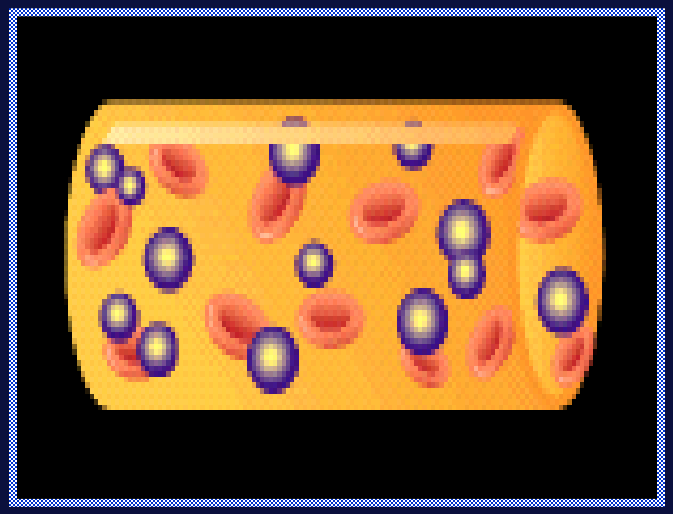
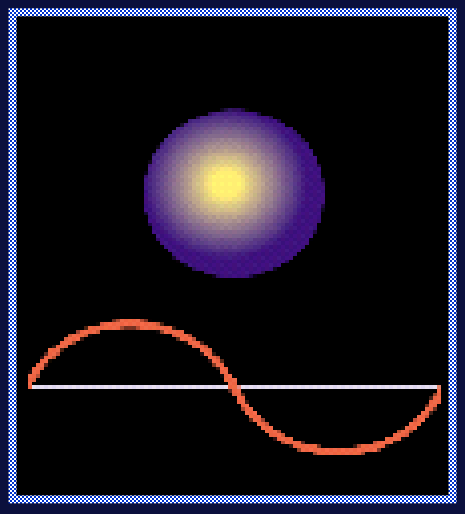
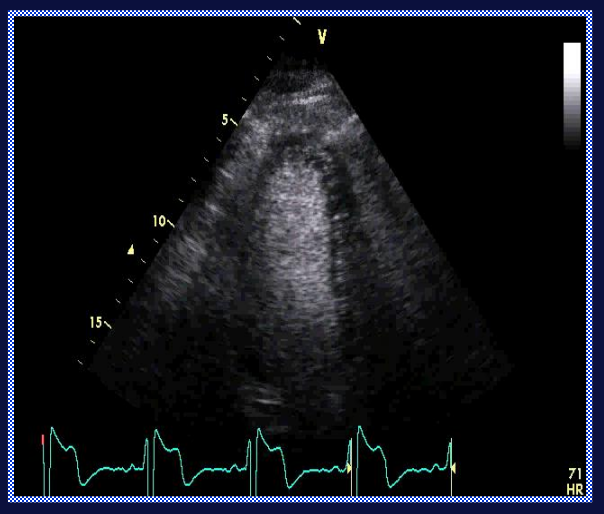
Contrast Echocardiography

Basics and Perfusion Imaging







Steven J. Lester, MD, FACC, FRCP(C), FASE
Mayo Clinic, Arizona

DISCLOSURE

Relevant Financial Relationship(s)

None

Off Label Usage

Perfusion

Non-Linear Oscillation of Ultrasound Contrast Microbubbles

a. Produce only a harmonic backscatter signal.
b. Produce only a backscatter signal the same as the insonating frequency.
c. Occurs when the microbubble expands and compresses to the same degree as in oscillates in harmony with the pressure waves of the ultrasound field.
d. Occurs only when the microbubbles are sized small enough to pass through the pulmonary capillaries and opacify left sided structures.
e. Is an acoustic behavior of a microbubble that supports real-time perfusion imaging.

Contrast Is Contraindicated in Patients with:

a. Pulmonary hypertension
b. Known intracardiac shunt
c. Unstable CHF
d. Hypersenstivity to the gas (perflutren)
e. b and d
f. All of the above

Microbubble Persistence Is Greatest with?

a. Smaller vs larger bubbles.
b. More compliant less-stiff microbubble shells.
c. High molecular weight based gas filled bubbles.
d. Air filled gas bubbles.
e. b and d

Computerized Tomography

Magnetic Resonance

Objectives

1. Define ultrasound contrast?
2. Recognize the interaction of the bubbles with ultrasound
3. Describe how contrast maximizes value
   - Incremental value for LVO
   - Incremental value for spectral Doppler
   - Tissue characterization
4. Explain how to set up the pictures/Pitfalls
5. Perfusion
6. Safety

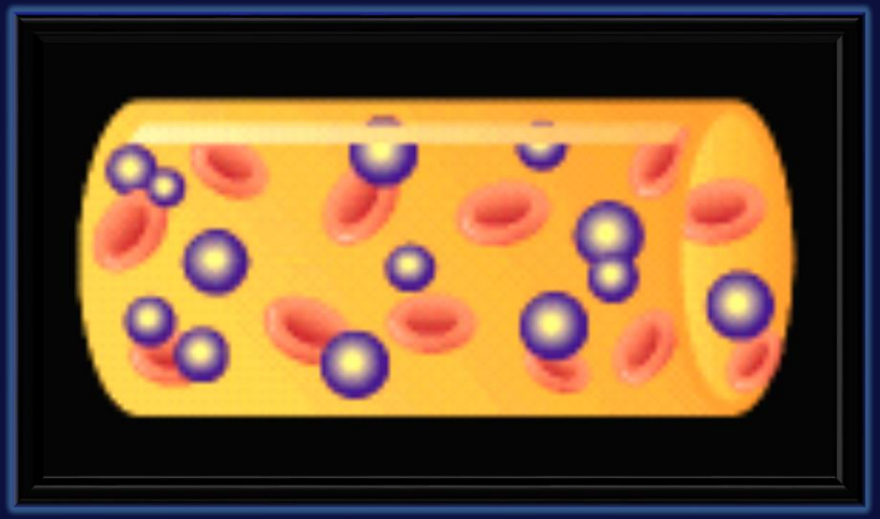
History

- Contrast enhancement with agitated saline solution or other fluids containing gas have been recognized for over 40 years.
- Bubbles of room air were either too big or dissolved too rapidly
- Therefore early contrast echocardiography was limited to shunt detection or the evaluation of right sided structures.

Cheng SC et al. *Am J Cardiol.* 1998;81:41G–48G.

Contemporary Ultrasound Contrast Agents

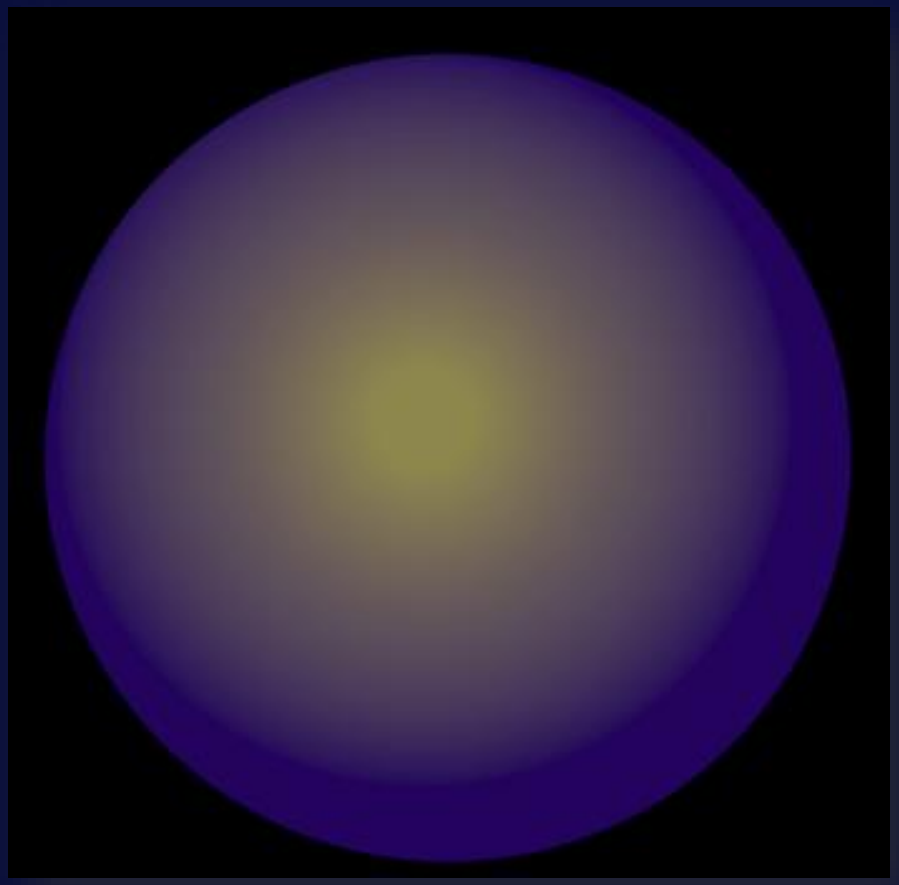
Stabilized gas microbubbles sized to pass through the smallest capillaries



FDA Approved Contrast Agents

Agent	Size (μm)	Gas	Shell	Indication
Optison	3.0-4.5	Perflutren	Albumin	LVO/EBD
Definity	1.3-3.3	Perflutren	Phospholipid	LVO/EBD
Lumason	1.5-2.5	Sulfur hexafloride	Phospholipid	LVO/EBD

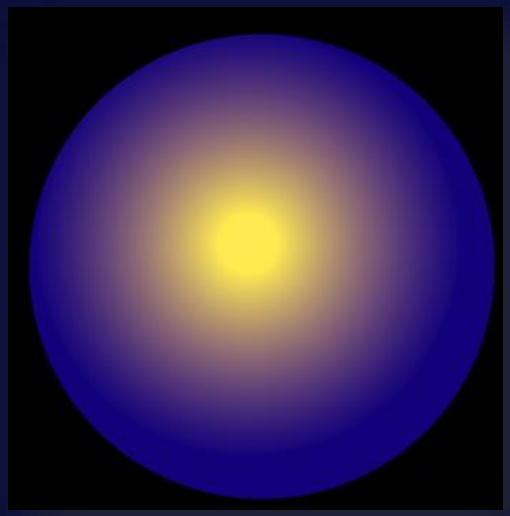
Bubble Characteristics



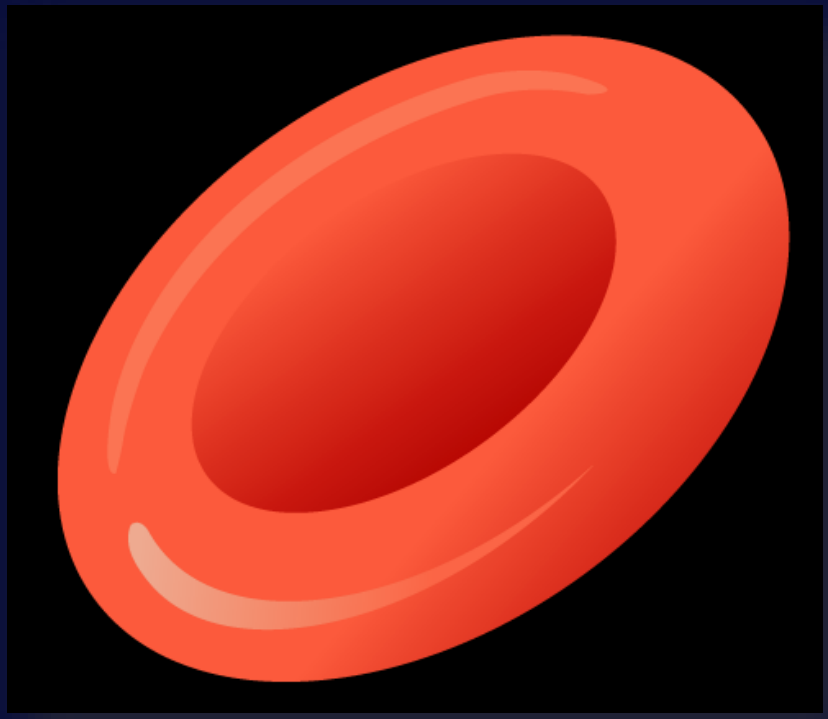
- Size
- Shell
- Gas

DeMaria. *Clin Cardiol*. 1997;20(suppl I):I-3.

Microbubbles - Size



Microbubble
2–8 µm



RBC
6–8 µm

Cheng et al. *Am J Cardiol.* 1998;81:41G.

Microbubbles - Shell

Shell Composition

- Proteins
- Biocompatible polymers
- Phospholipids

Shell Properties

- Elasticity
- Fragility
- Biodistribution
- Elimination

Burns PN. In: Rumack CM et al, eds. *Diagnostic Ultrasound*. Vol. 1. 2nd ed. St. Louis, MO: Mosby; 1998:57.

Microbubbles - Gas

Air

- Highly soluble
- Low persistence and stability
- Rapid diffusion after disruption

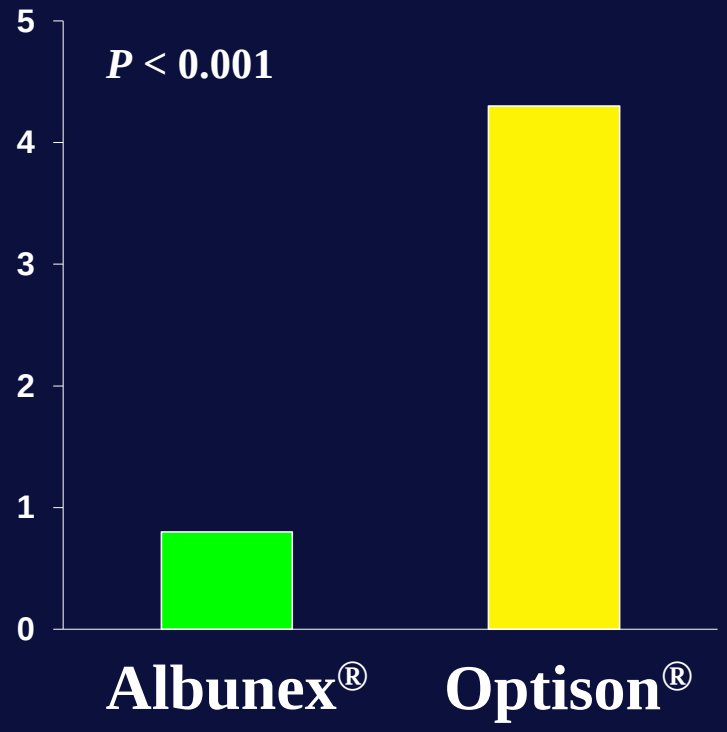
Heavy Gases

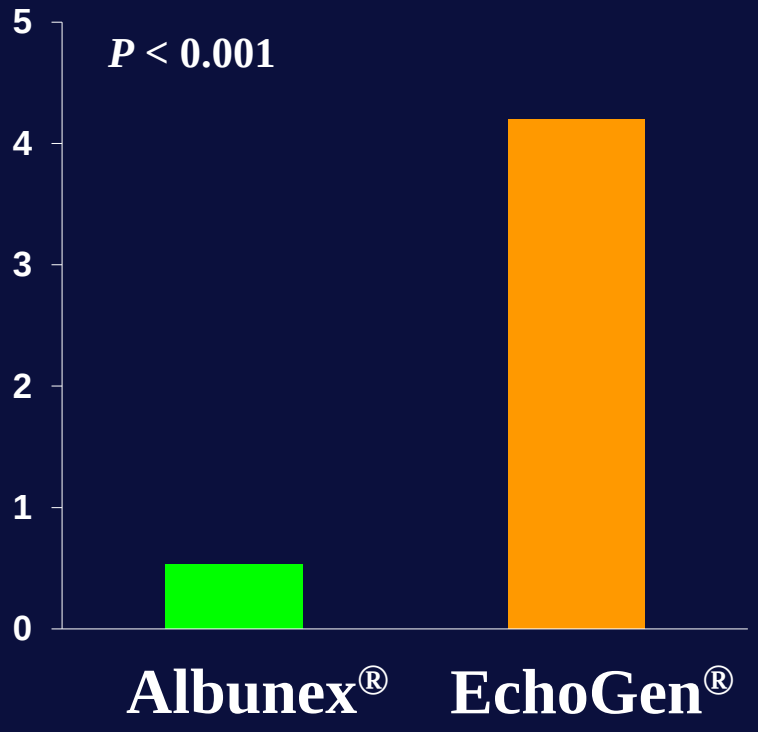
- High molecular weight
- Low solubility
- High persistence and stability
- Inert & safe

Villarraga et al. *Tex Heart Inst J.* 1996;23:90.

Persistence: HMWG-Based Agents vs Albunex®

Duration of clinically useful contrast effect (min)





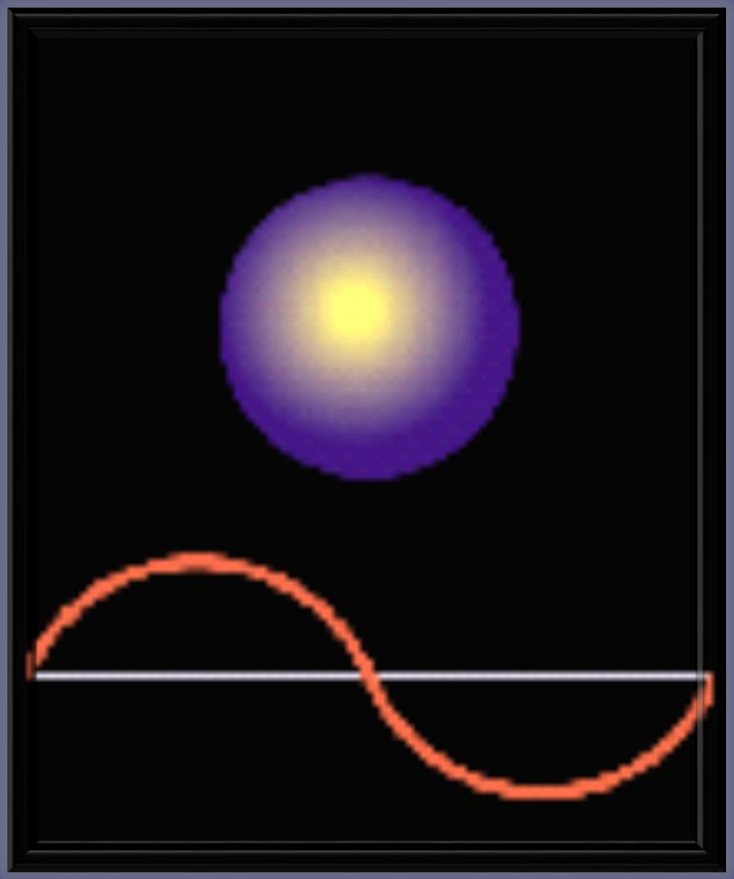
Adapted from Cohen et al. *J Am Coll Cardiol.* 1998;32:746.

Adapted from Grayburn et al. *J Am Coll Cardiol.* 1998;32:230.

Bubble Behavior in an Ultrasound Field

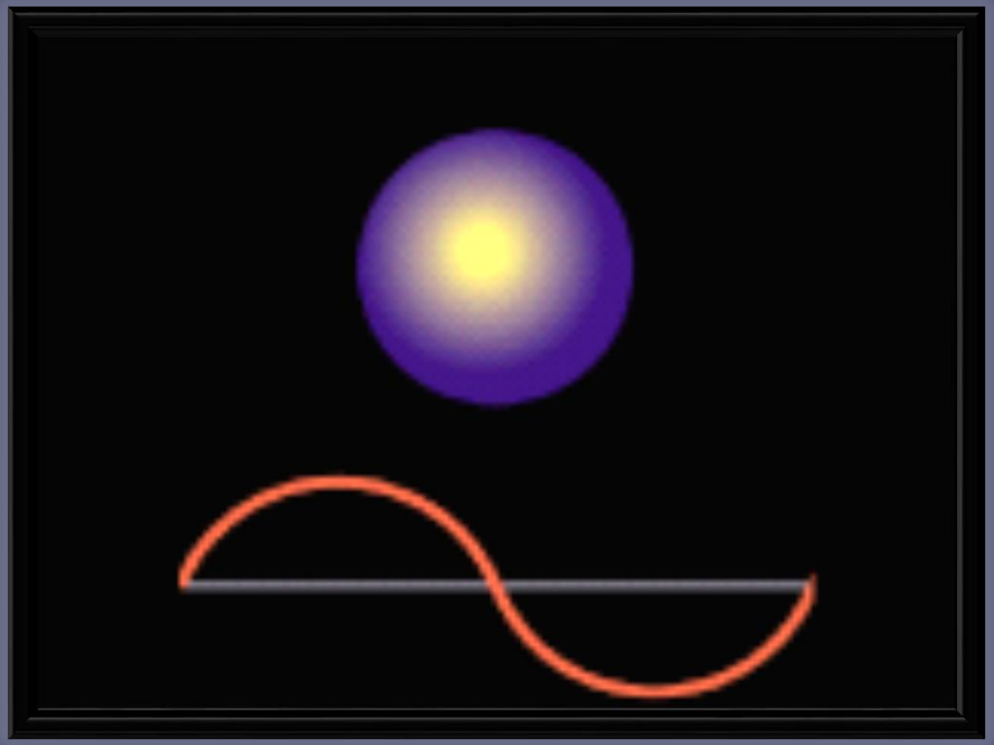
MI	Bubble Behavior	Acoustic Behavior	Clinical Application
< 0.1	Linear Oscillation	Backscatter Enhancement	Fundamental LVO Spectral Doppler
0.1-1.0	Nonlinear Oscillation	Harmonic Backscatter	Harmonic LVO Real time perfusion
>1.0	Disruption	Transient Harmonic Echos	Doppler LVO Triggered perfusion

Response of Bubbles to Ultrasound: Linear Resonance

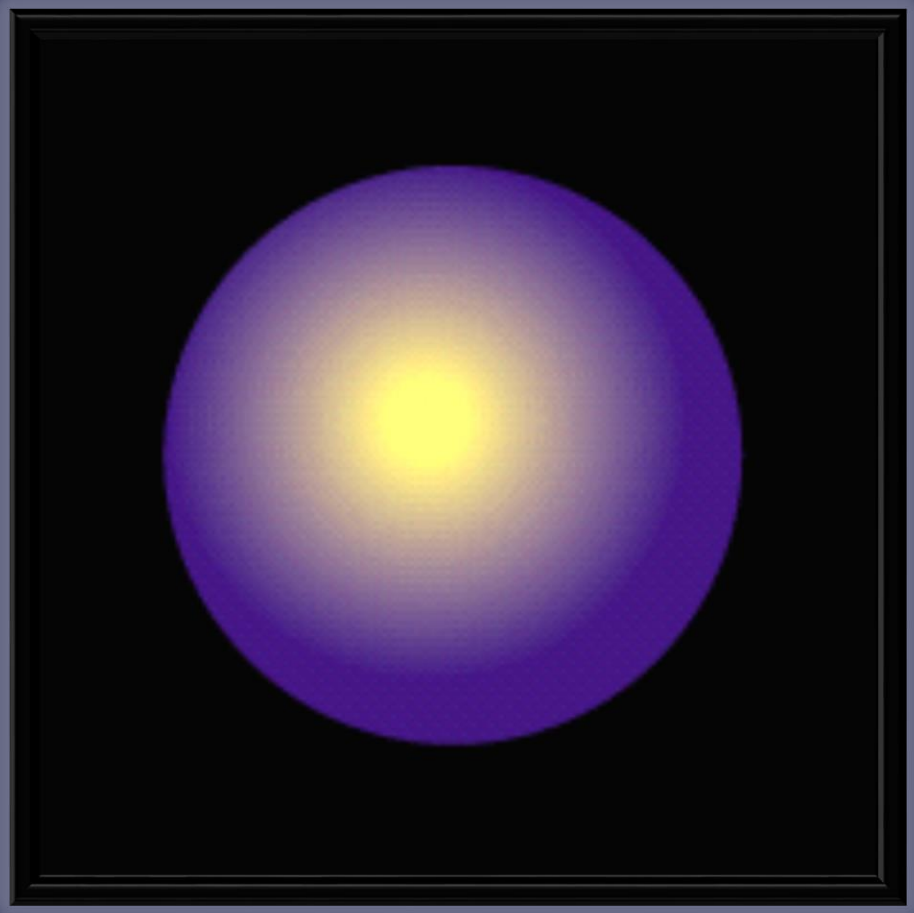


P. Burns & H. Becher. *Handbook of Contrast Echocardiography: LV Function and Myocardial Perfusion.* Springer; 2000.

Response of Bubbles to Ultrasound: Nonlinear Resonance



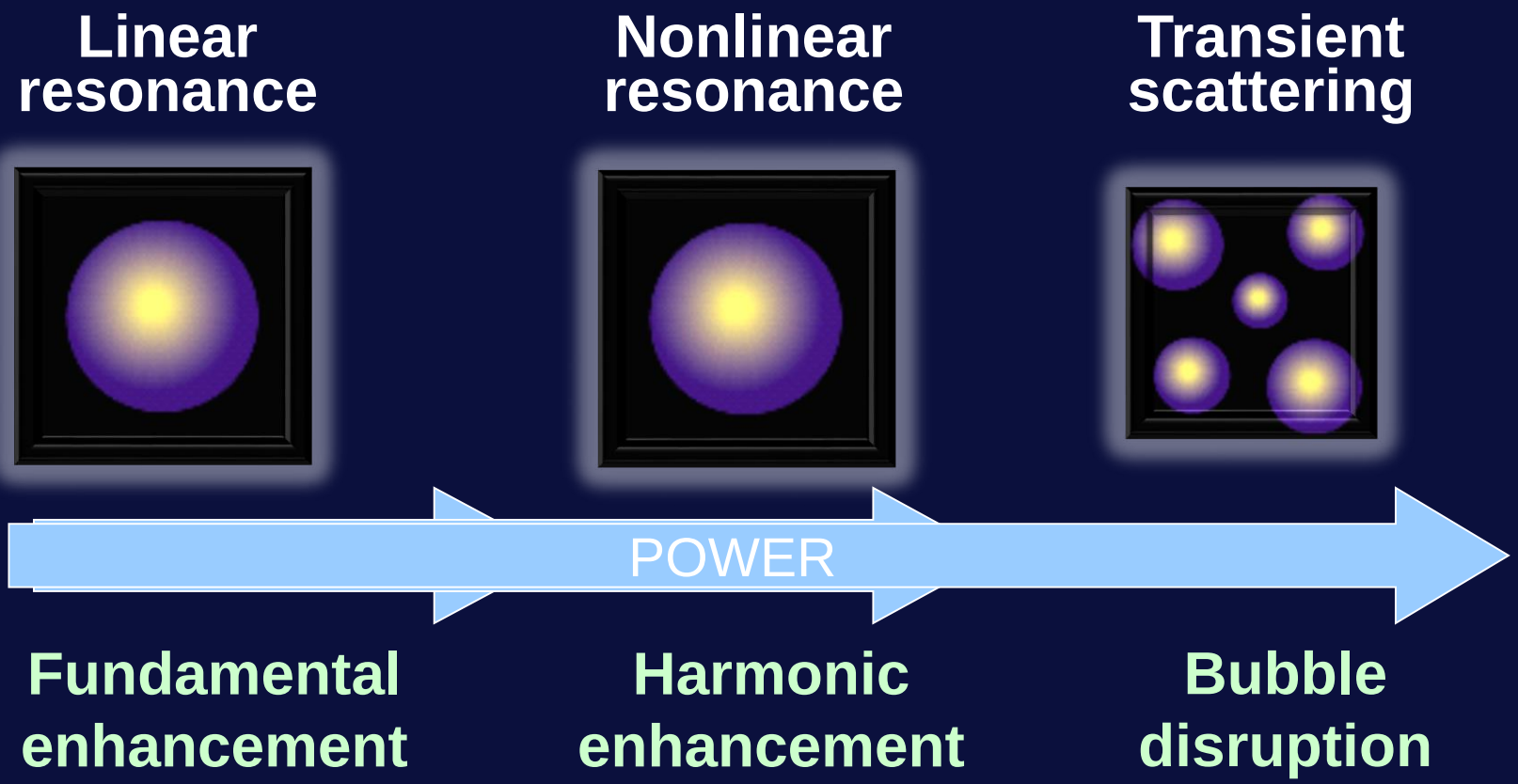
Response of Bubbles to Ultrasound: Transient Scattering



Very strong nonlinear backscatter of extremely short duration

Wei et al. *J Am Coll Cardiol.* 1997;29:1081.

Interaction of Ultrasound and Microbubbles



Burns PN. *Echocardiography*. 2002;19:241–258.

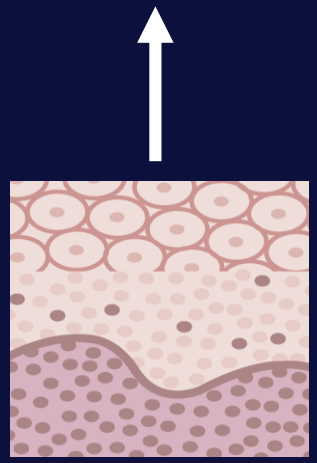
Principles of Harmonic Imaging

- Tissue and blood reflect at the fundamental frequency

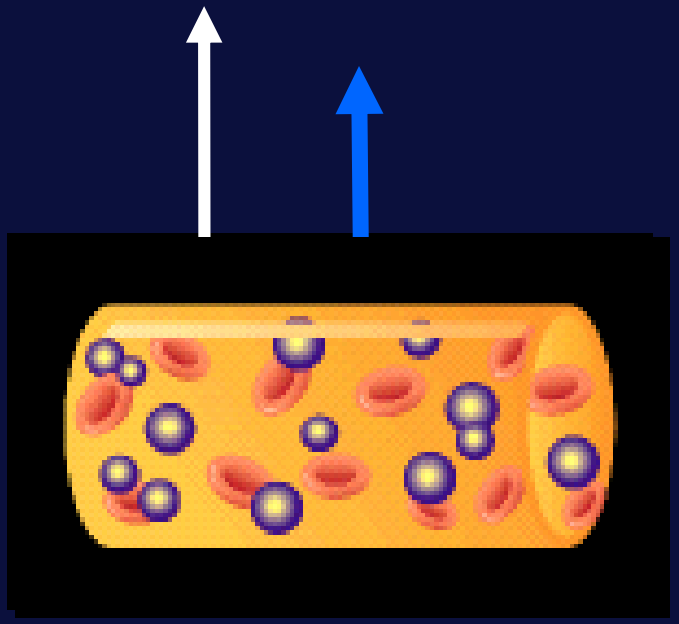
2.5 MHz

- Microbubbles reflect at both the fundamental and the harmonic frequencies

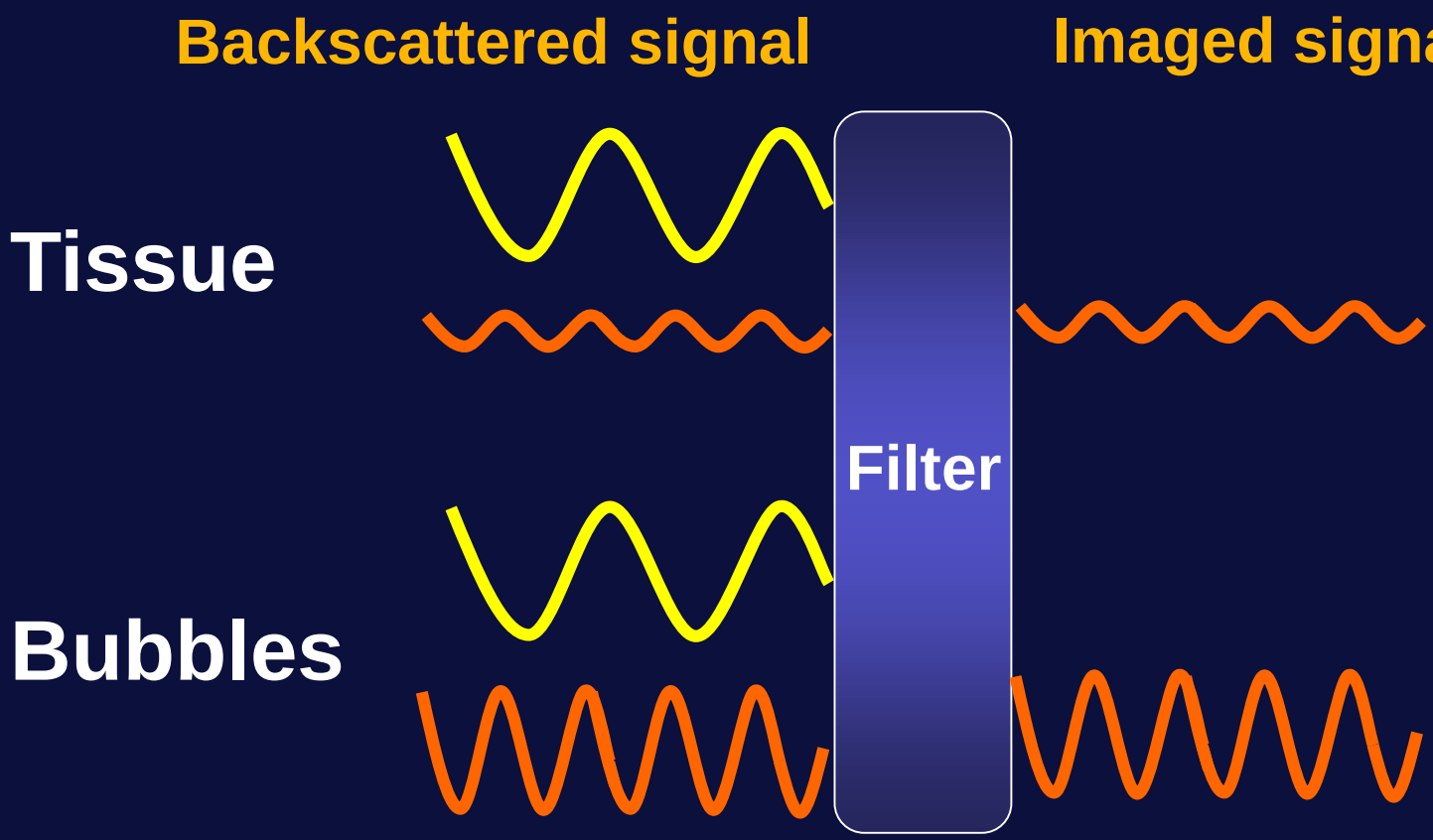
2.5 MHz



2.5 MHz + 5 MHz



Harmonic Imaging: Signal Filtering



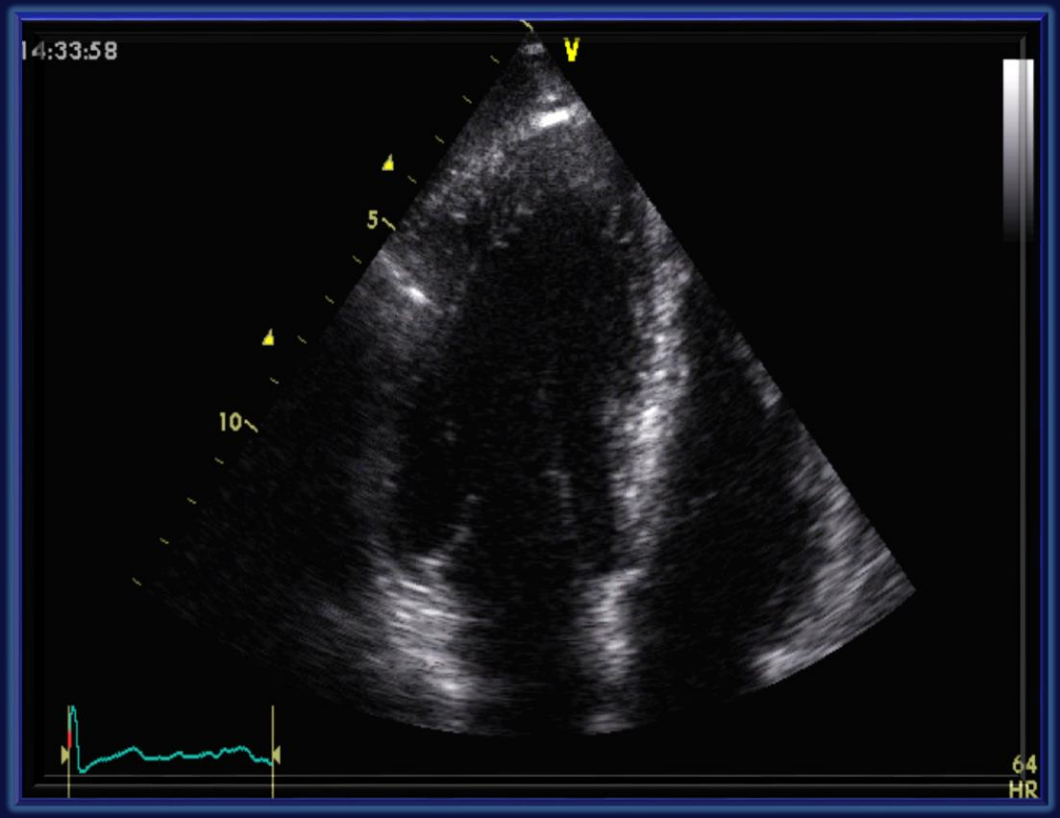
Burns. In Rumack et al, eds. *Diagnostic Ultrasound*. Vol. 1. 2nd ed. St. Louis: Mosby; 1998:57.

Objectives

1. What is ultrasound contrast?
2. Understand the interaction of the bubbles with ultrasound
3. Contrast maximizes value
   - Incremental value for LVO
   - Incremental value for spectral Doppler
   - Tissue characterization

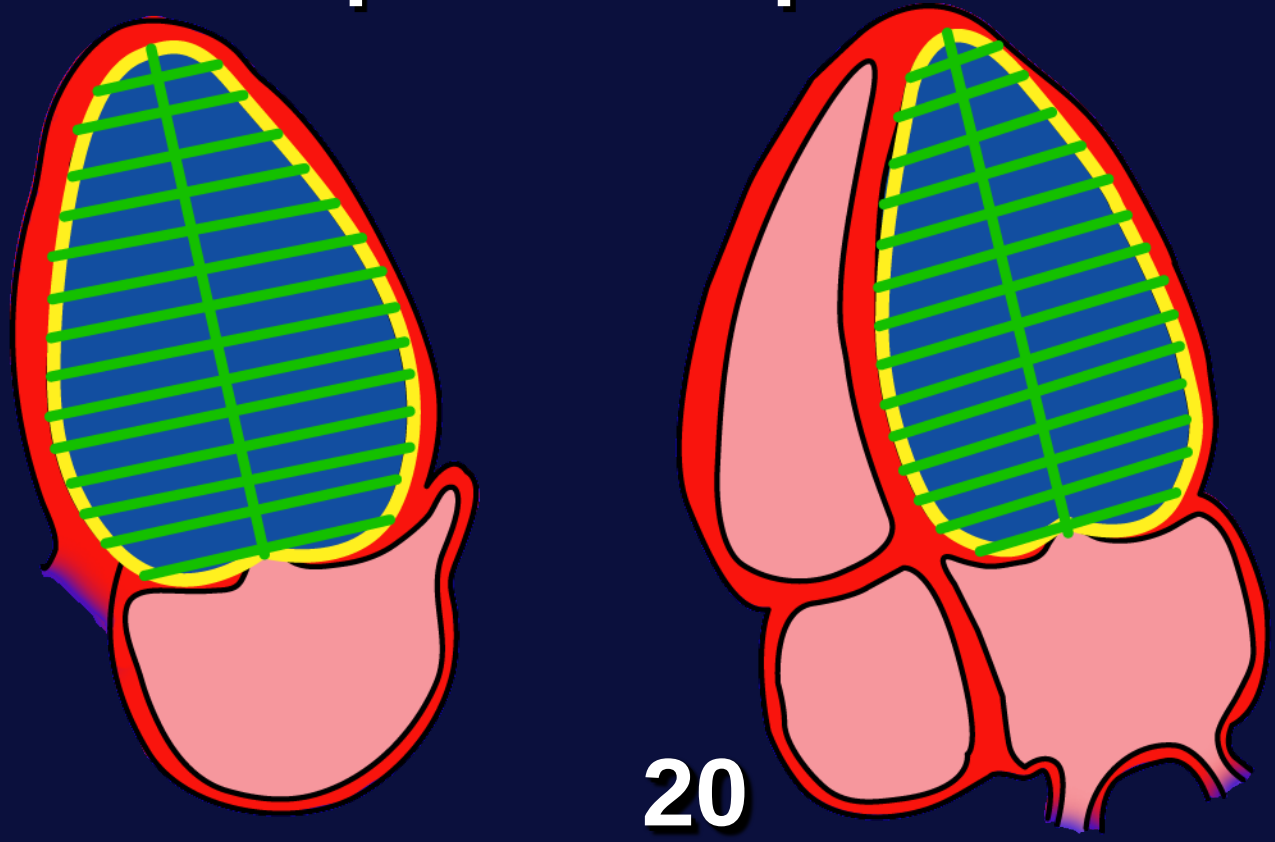
Echocardiography and Left Ventricular Function

- Most common use of diagnostic echocardiography
- Global ventricular function
- Regional wall motion
  - Rest
  - Stress

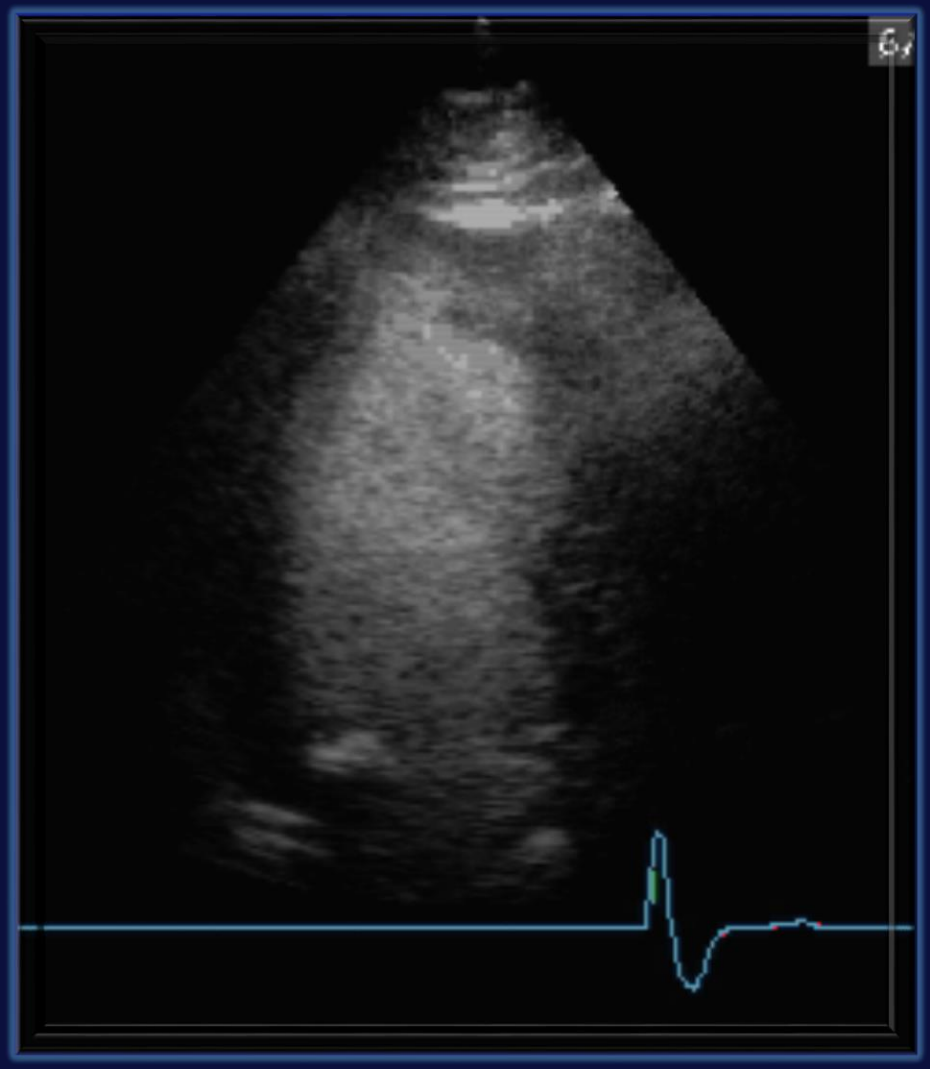


Left Ventricular Volume

Modified Biplane Simpson's Method

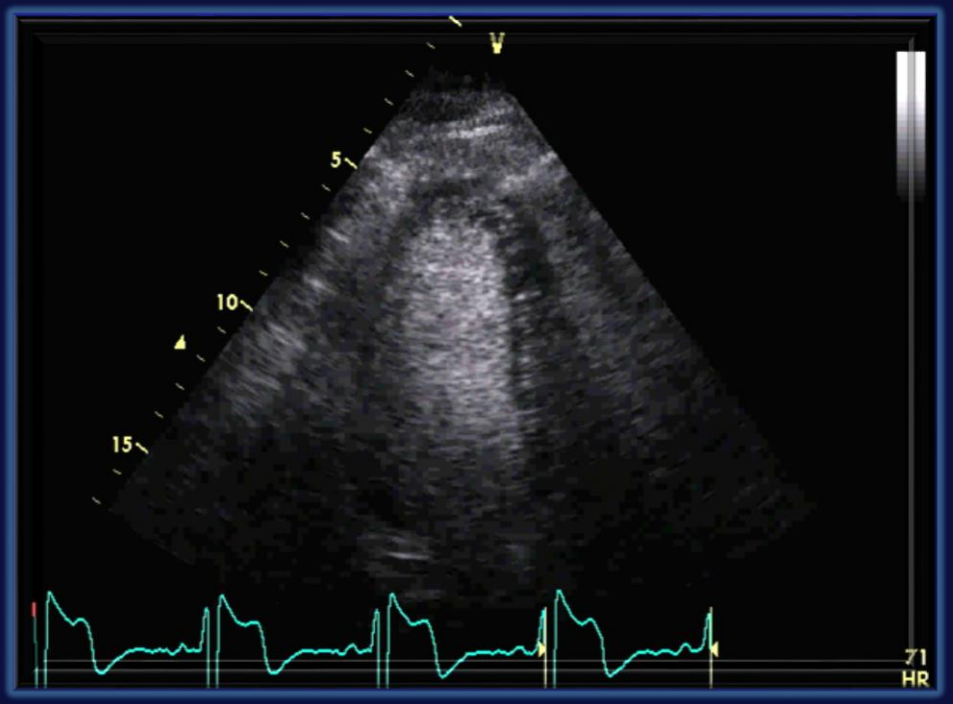


$$\text{Biplane volume} = \frac{\pi}{4} \sum_{i=1}^{20} a_i b_i \cdot \frac{L}{20}$$

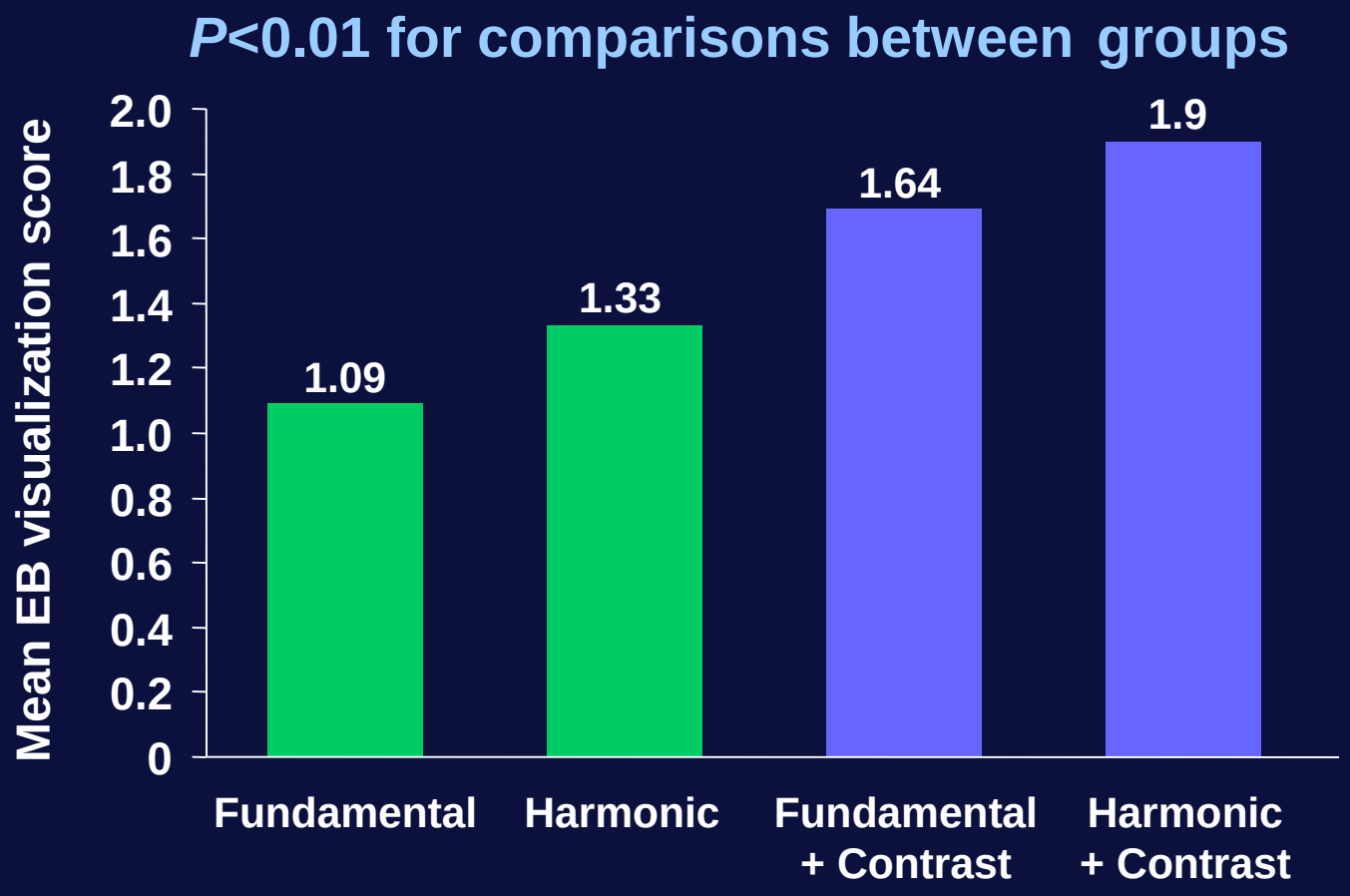


Contrast Echocardiography

- Increased sensitivity
- Heightened diagnostic confidence
- Improved accuracy and reproducibility
- Enhanced clinical utility



Use of Contrast and Harmonic Imaging

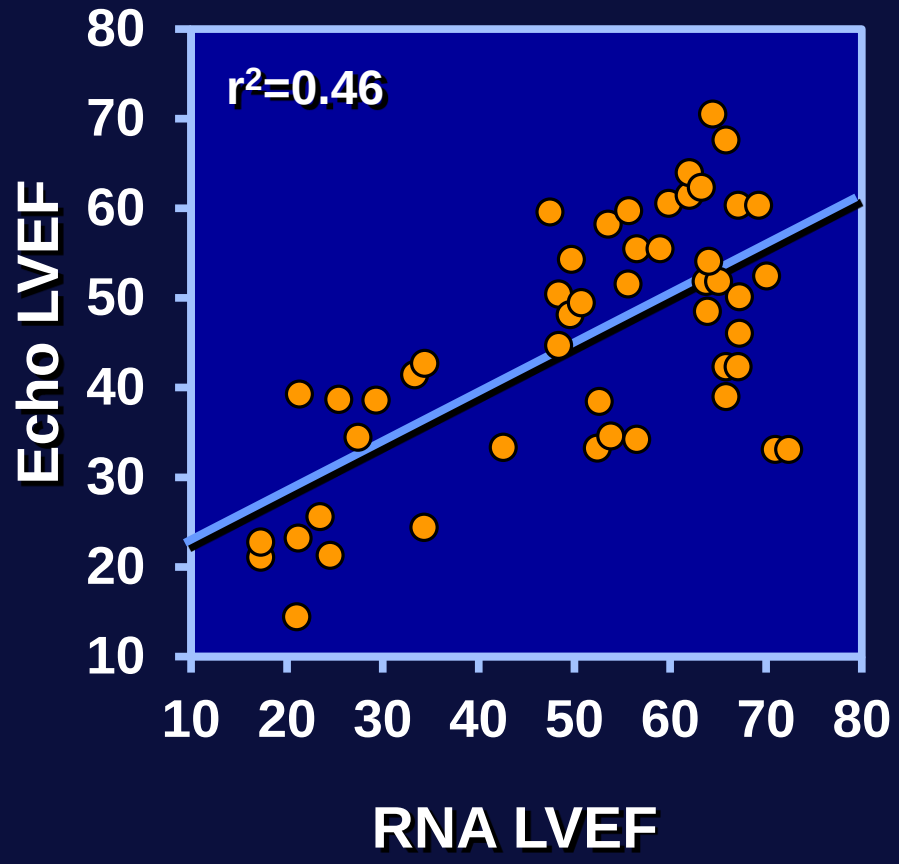


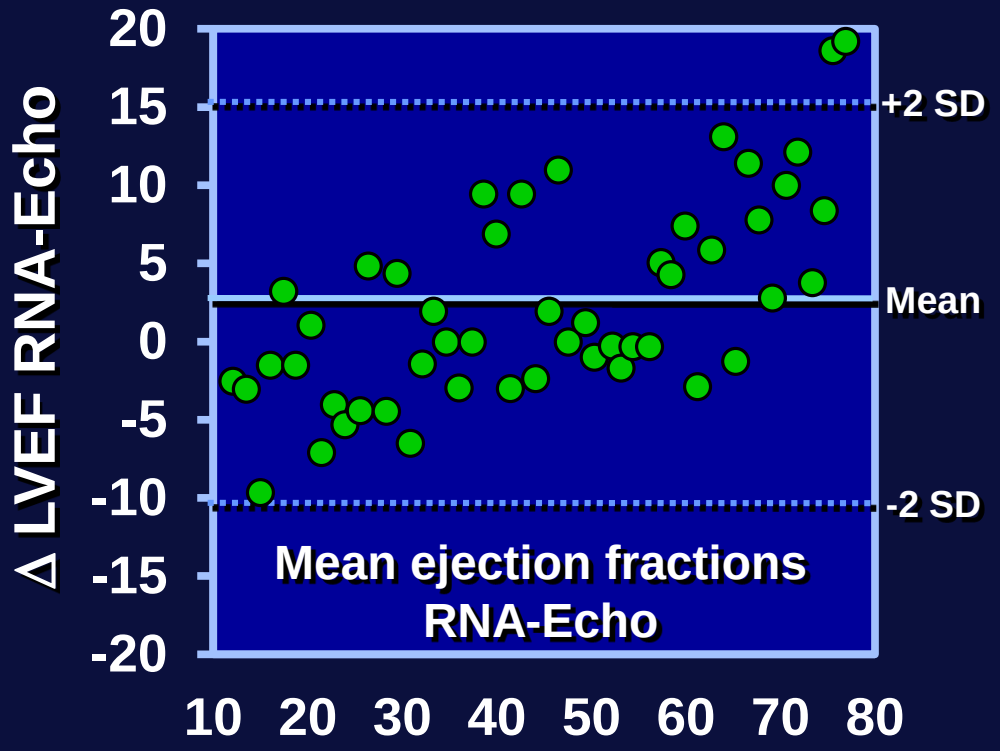
Daniel et al. *J Am Soc Echocardiogr*. 2001;14:917.

LV Ejection Fraction

Echo Modified Biplane Simpson's Method vs. RNA

Fundamental Imaging

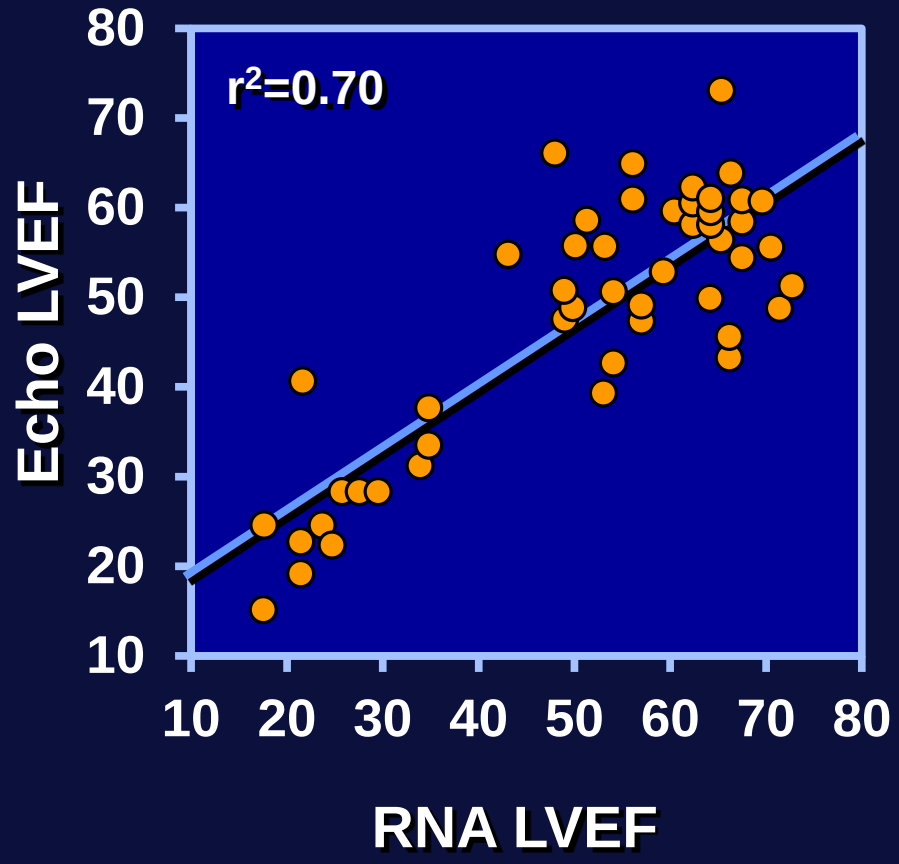


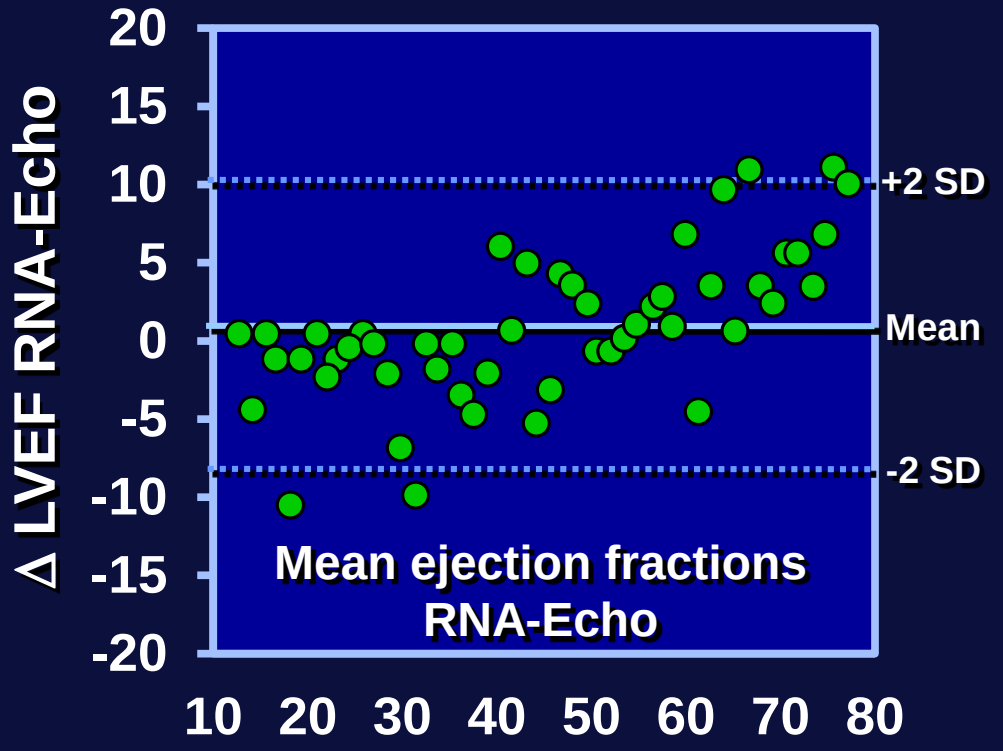


Nahar T et al: Am J Cardiol 86:1358, 2000

LV Ejection Fraction

Echo Modified Biplane Simpson's Method vs. RNA Harmonic Imaging



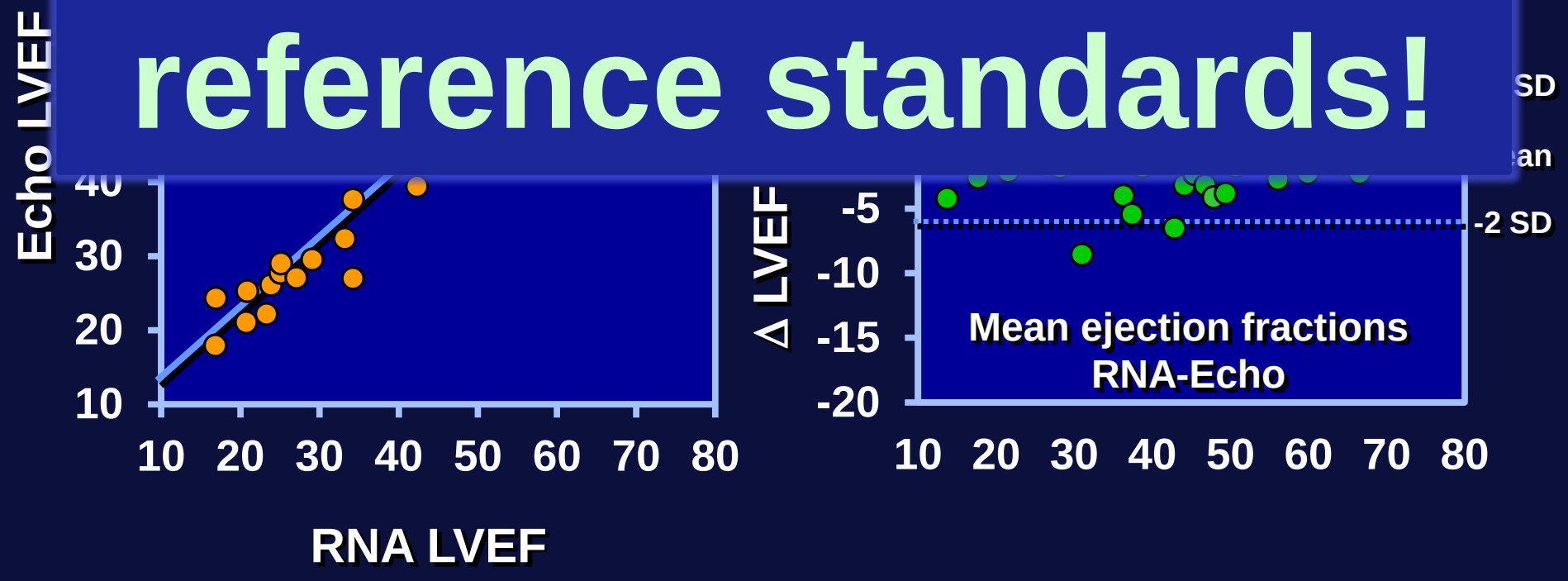


Nahar T et al: Am J Cardiol 86:1358, 2000

LV Ejection Fraction

Echo Modified Biplane Simpson's Method vs. RNA Harmonic Imaging with Contrast

Better correlation with reference standards!



Nahar T et al: Am J Cardiol 86:1358, 2000

Determination of LV Volumes and Ejection Fraction with a HMWG-Based Agent

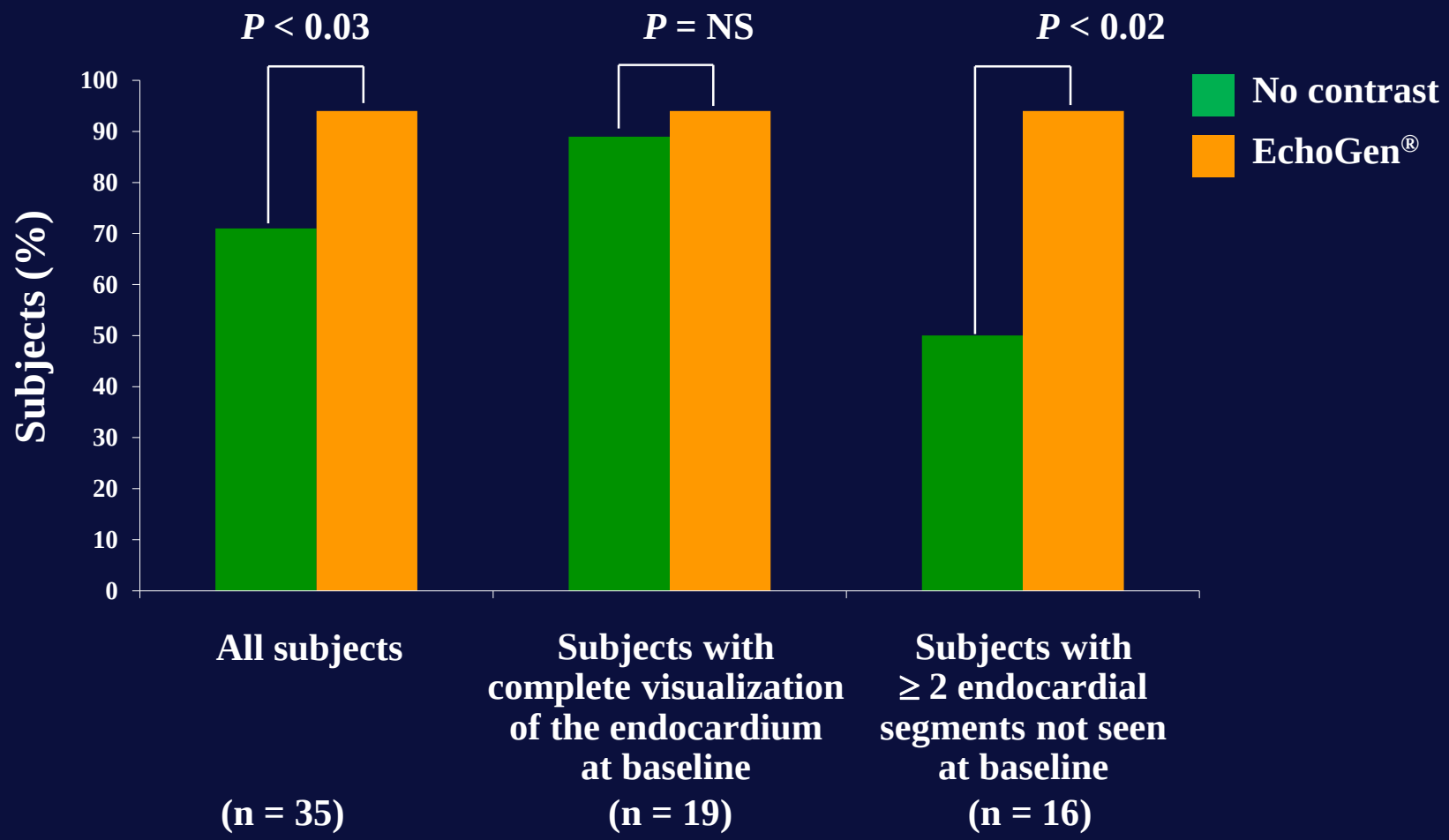
Absolute Difference Between Echocardiographic and Magnetic Resonance Imaging Measurements

	Standard Echo-MRI	Contrast Echo-MRI	*P* Value
End diastolic volume (mL)	21 ± 13	15 ± 14	0.038
End systolic volume (mL)	17 ± 13	12 ± 9	0.015
LVEF	0.08 ± 0.06	0.05 ± 0.03	0.031

All values are mean ± 1 SD.

Adapted from Hundley et al. *J Am Coll Cardiol*. 1998;32:1426.

Correct Classification of LV Systolic Function with Contrast



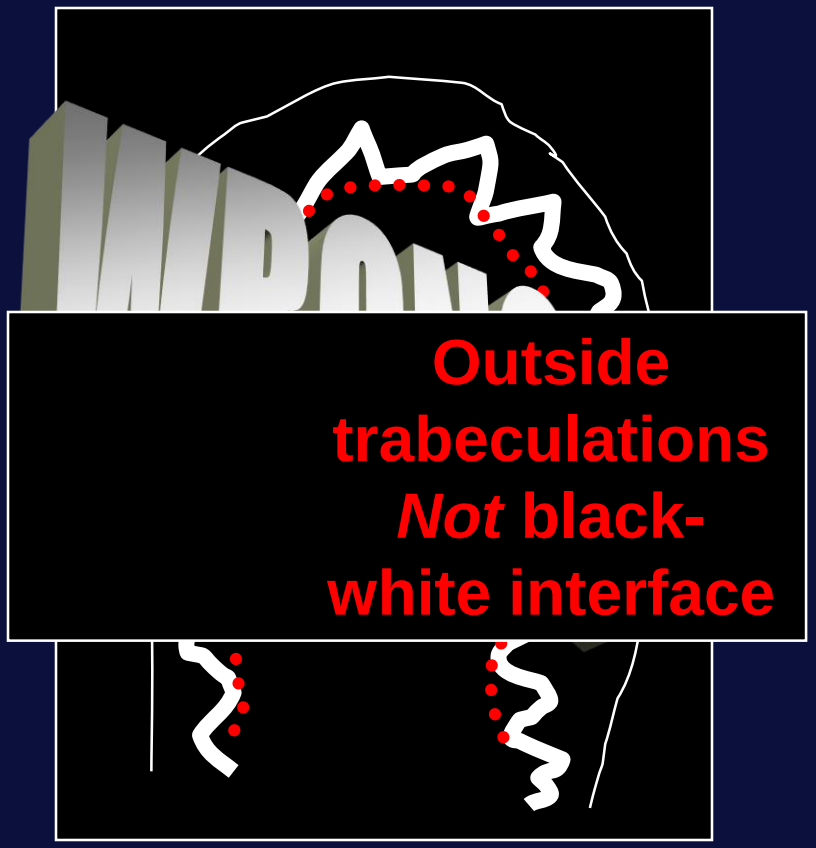
Adapted from Hundley et al. *J Am Coll Cardiol.* 1998;32:1426.

Contrast For LVO

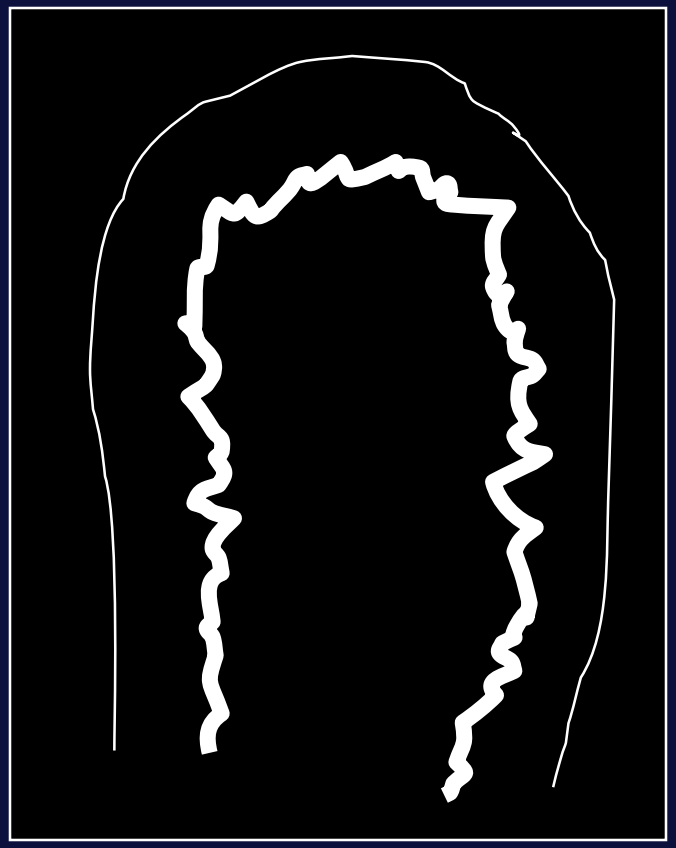
Take Home Points

1. Defines the endocardial border better than unenhanced echocardiography.
2. The underestimation of cardiac volumes by echocardiography is nearly resolved when contrast agents are used.
3. Reduced intra and interobserver variability in measures of LV volumes and EF with better correlation with reference standards.
4. Recommended for use with ≥ 2 LV segments are not well visualized.

Left Ventricular Volume
2D trace method

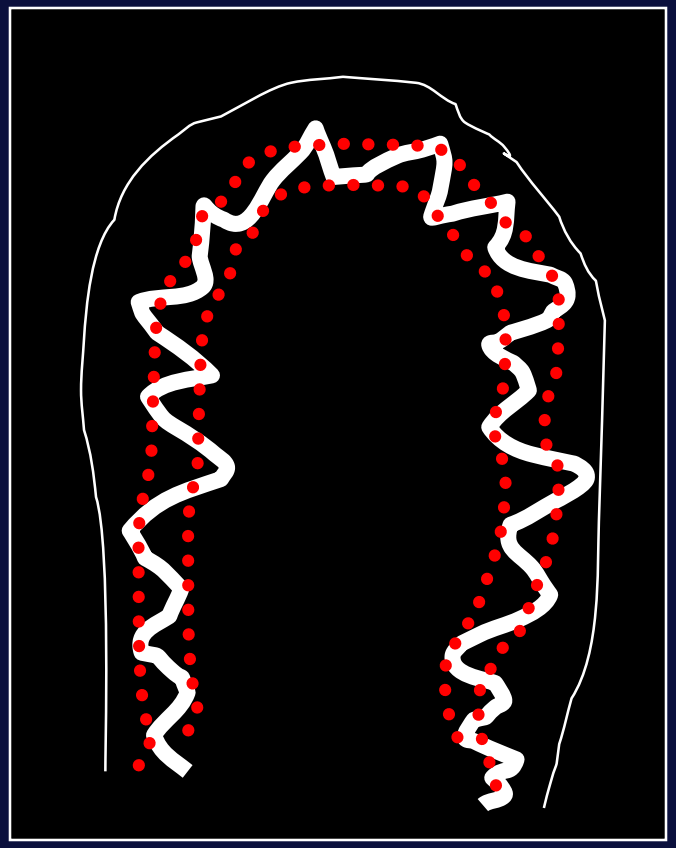


Diastole

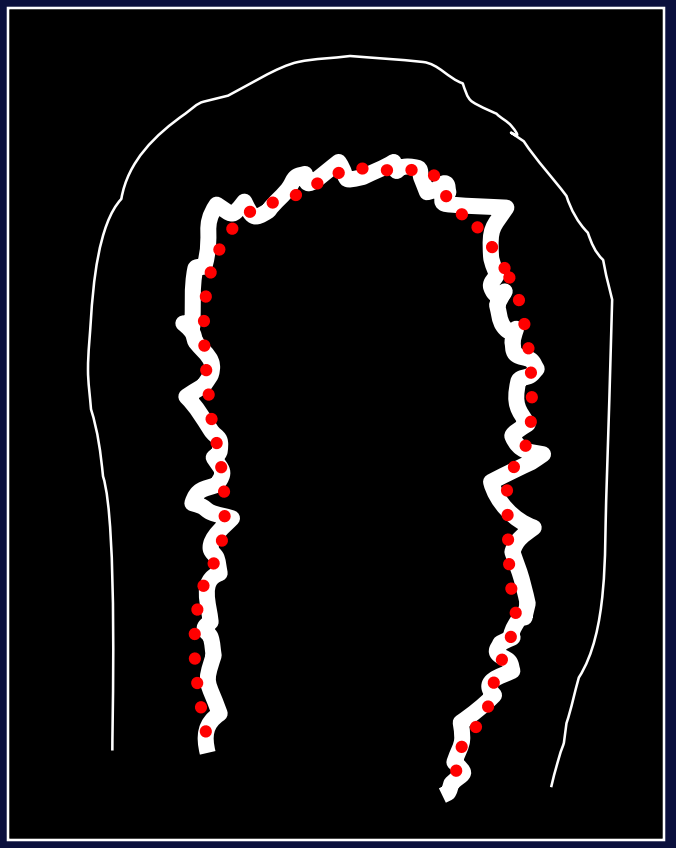


Systole

Left Ventricular Volume
2-D trace method



Diastole



Systole

End-Diastolic Volume

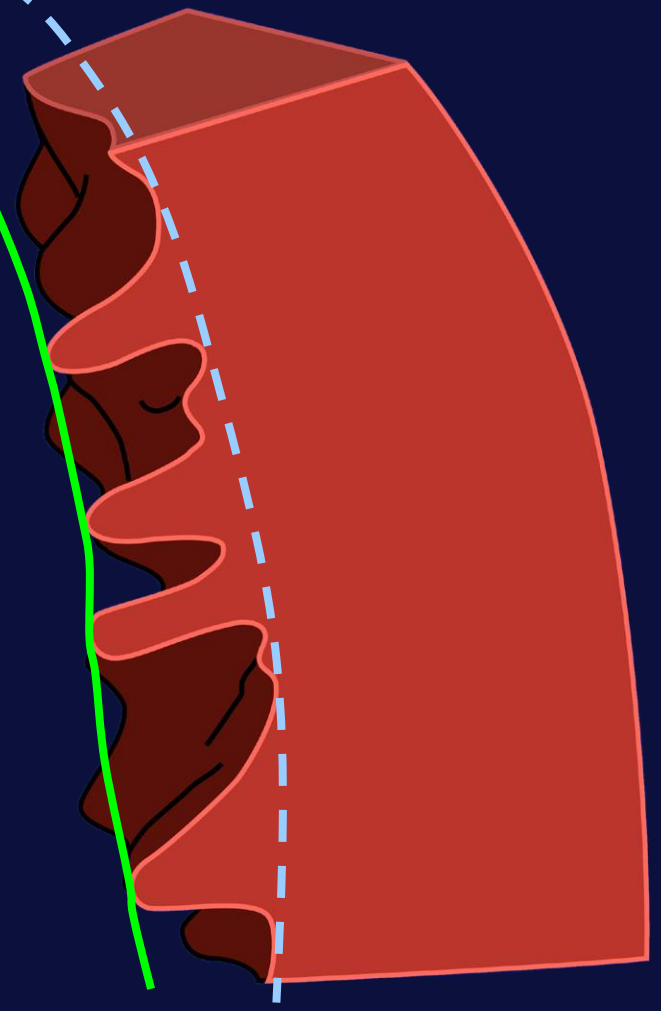
Trace Outside the Trabecular Margins

Left Ventricular Volume by 2-D Echo

Myocardial Border Detection vs Angiography

Angio outline

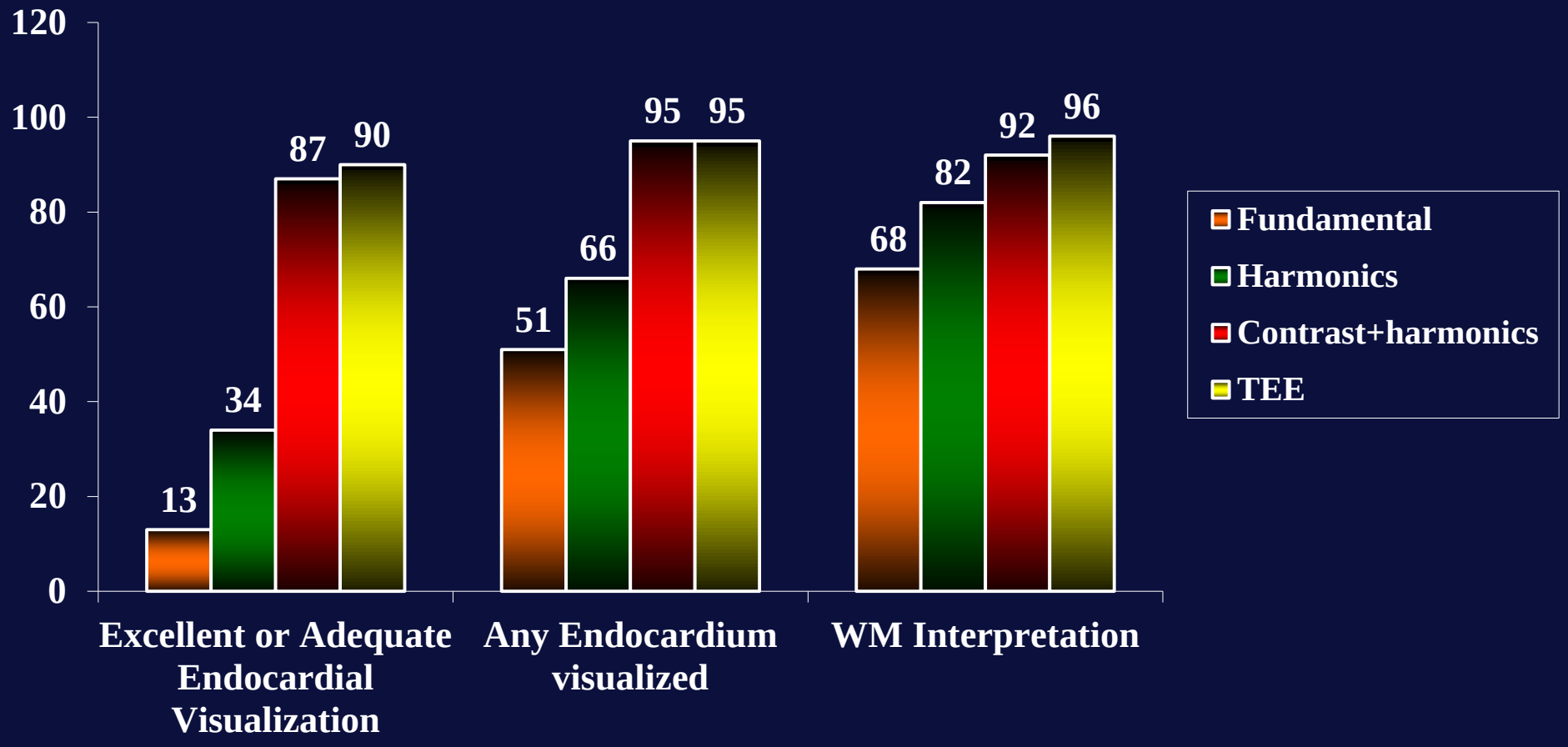
Echo outline
(no contrast)



Columnae carnae bases enclosed by angiographic dye vs apices imaged by ultrasound

Schnittger I et al: Am J Cardiol 50:512, 1982

Contrast Echocardiography In The ICU



Am J Cardiol 2002;89:711-718

Contrast For LVO

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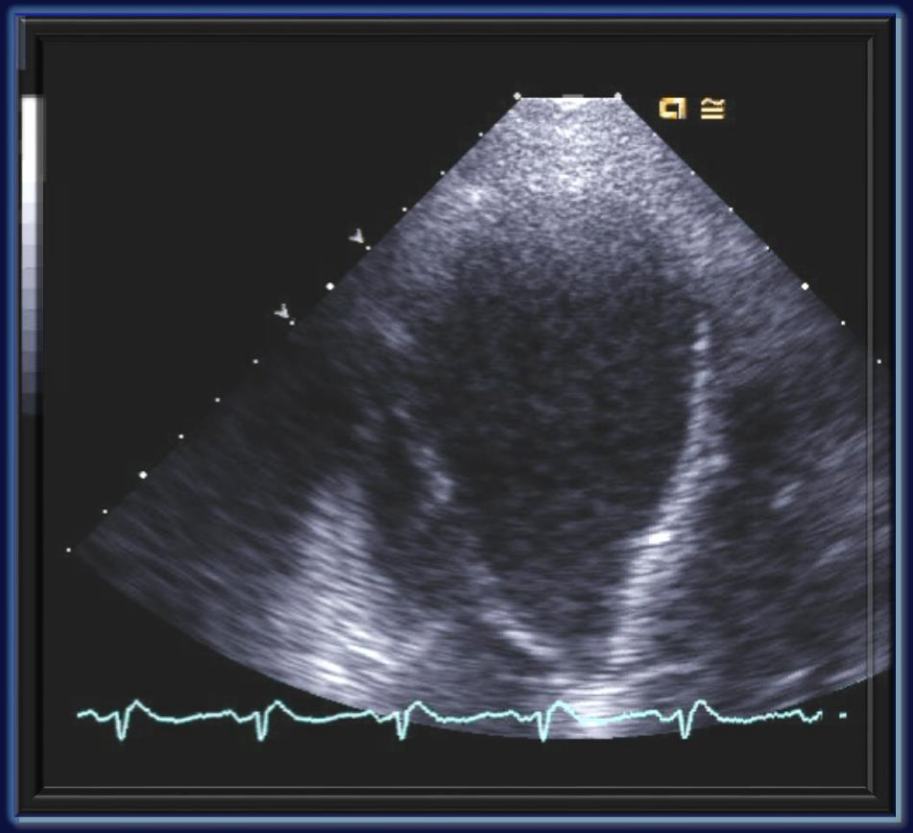
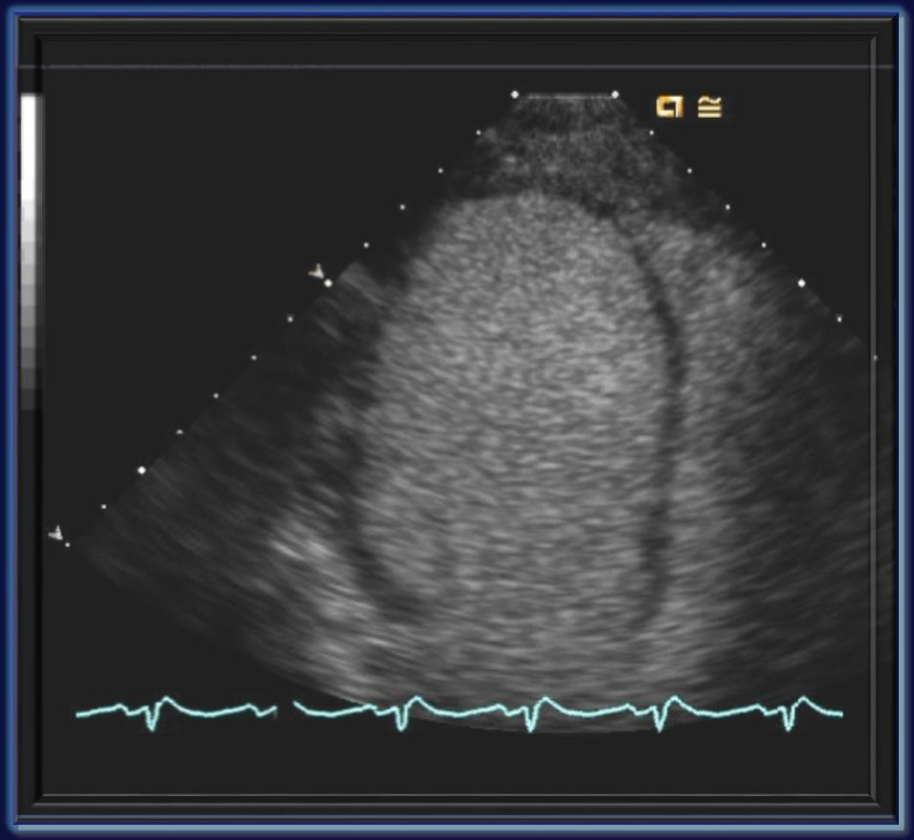
3. Reduced intra and interobserver variability in measures of LV volumes and EF with better correlation with reference standards.
4. Recommended for use when ≥ 2 LV segments are not well visualized.

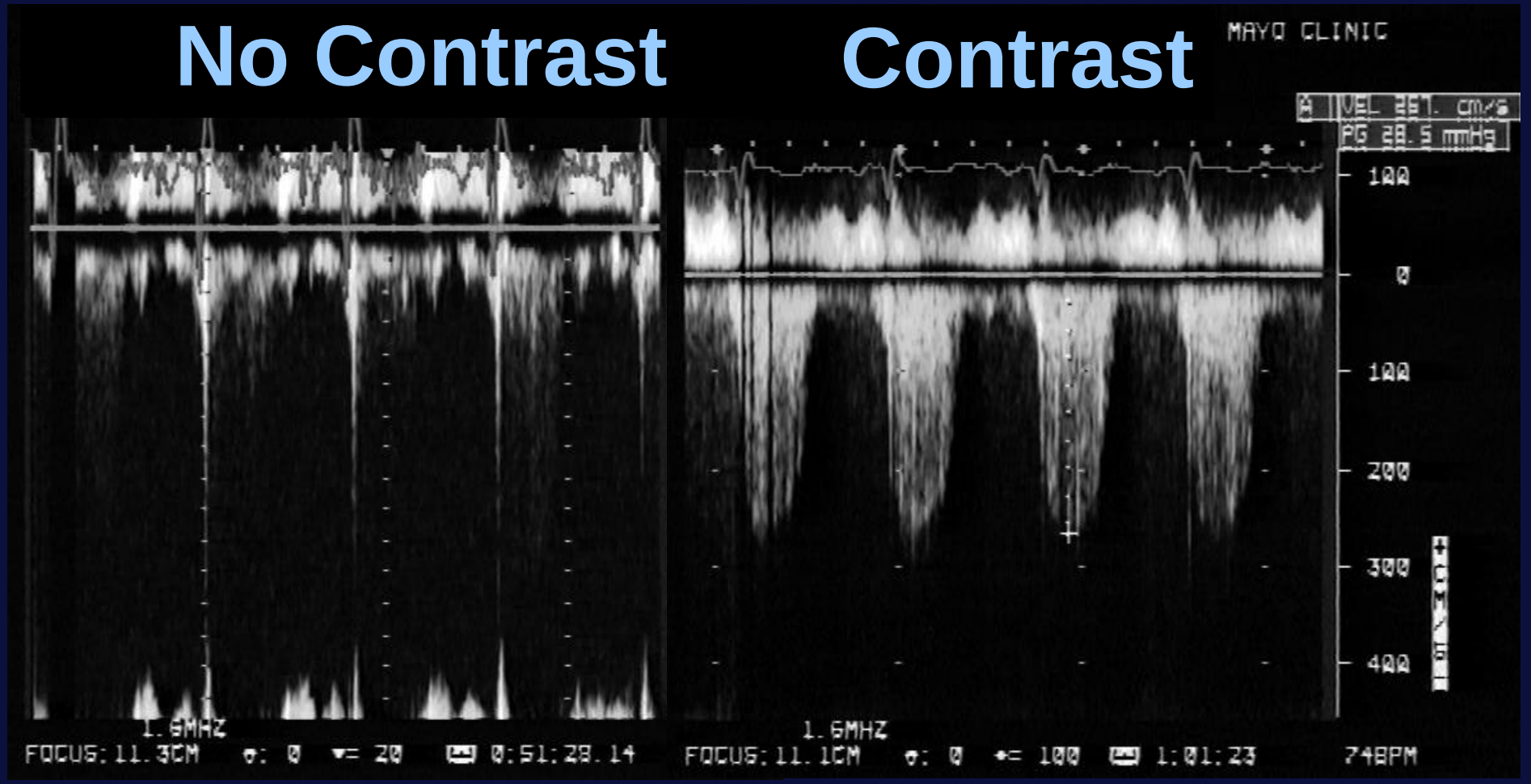
Why settle for this?



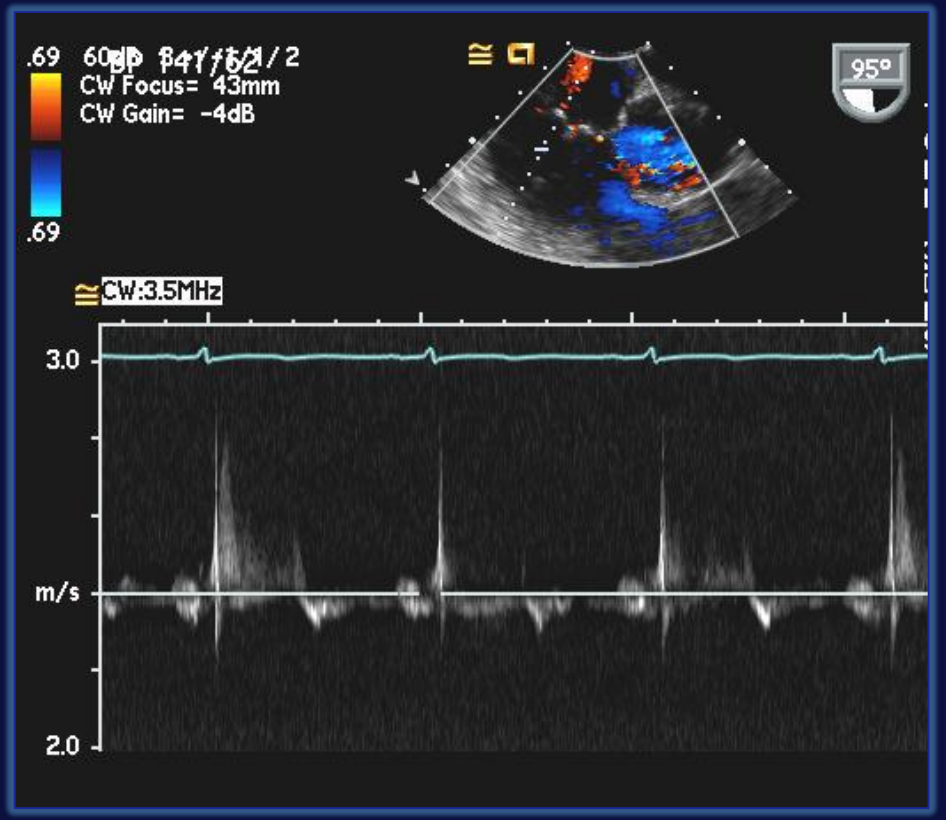
When you can have this!



Spectral Doppler Enhancement

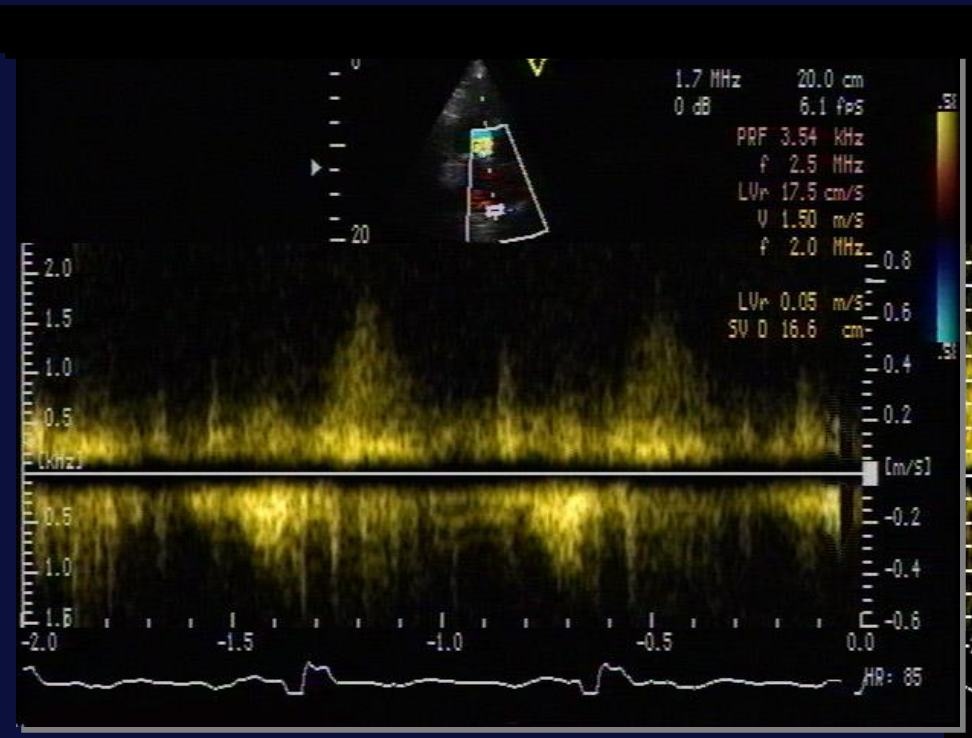


TEE TR: Contrast

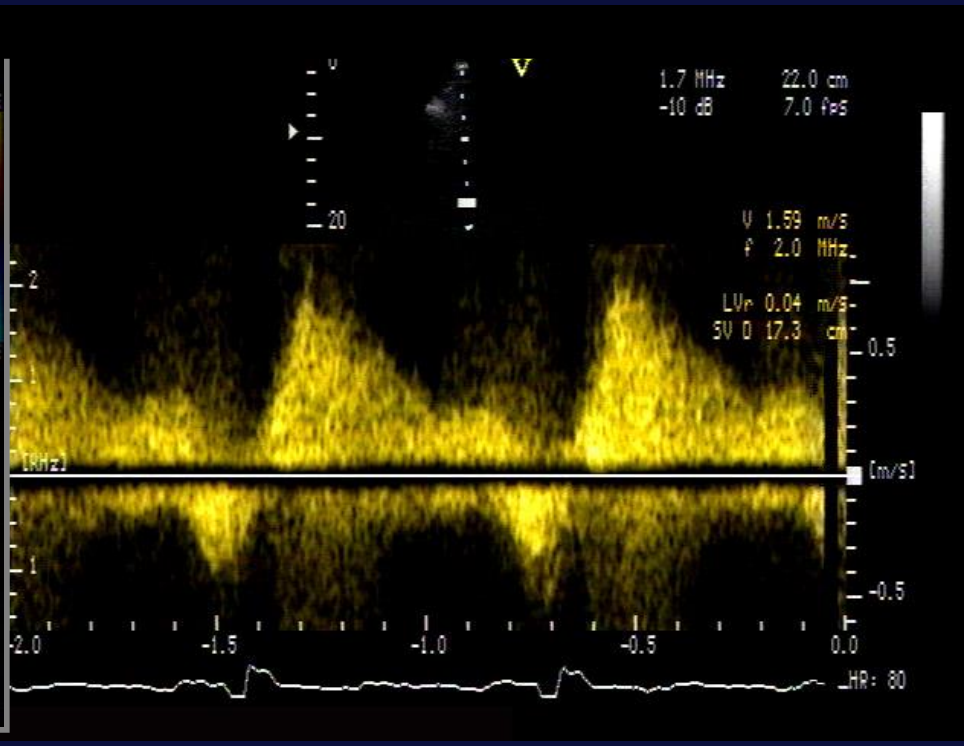


PULMONARY VEIN FLOW

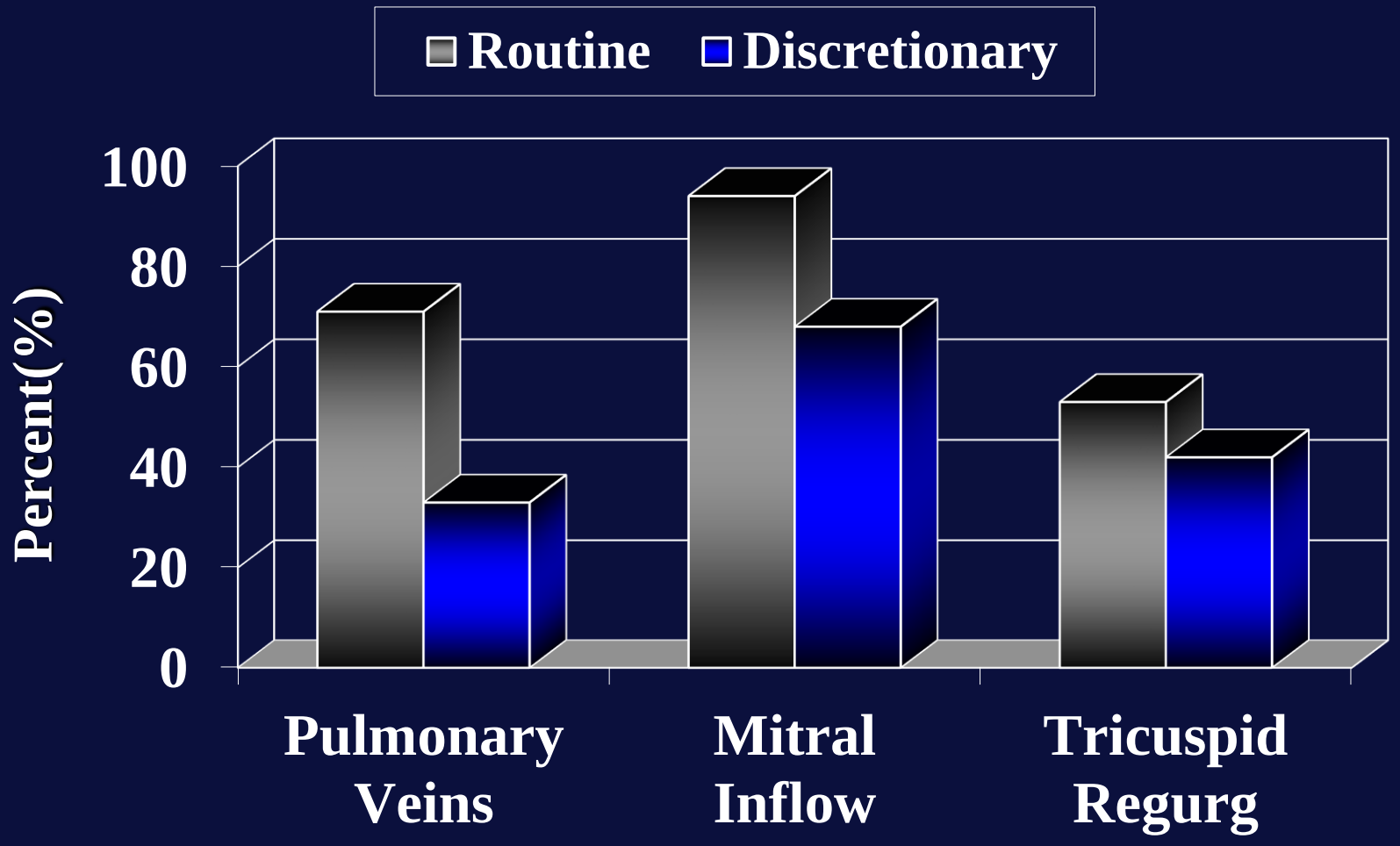
Without Contrast



With Contrast



Spectral Doppler Score = 1



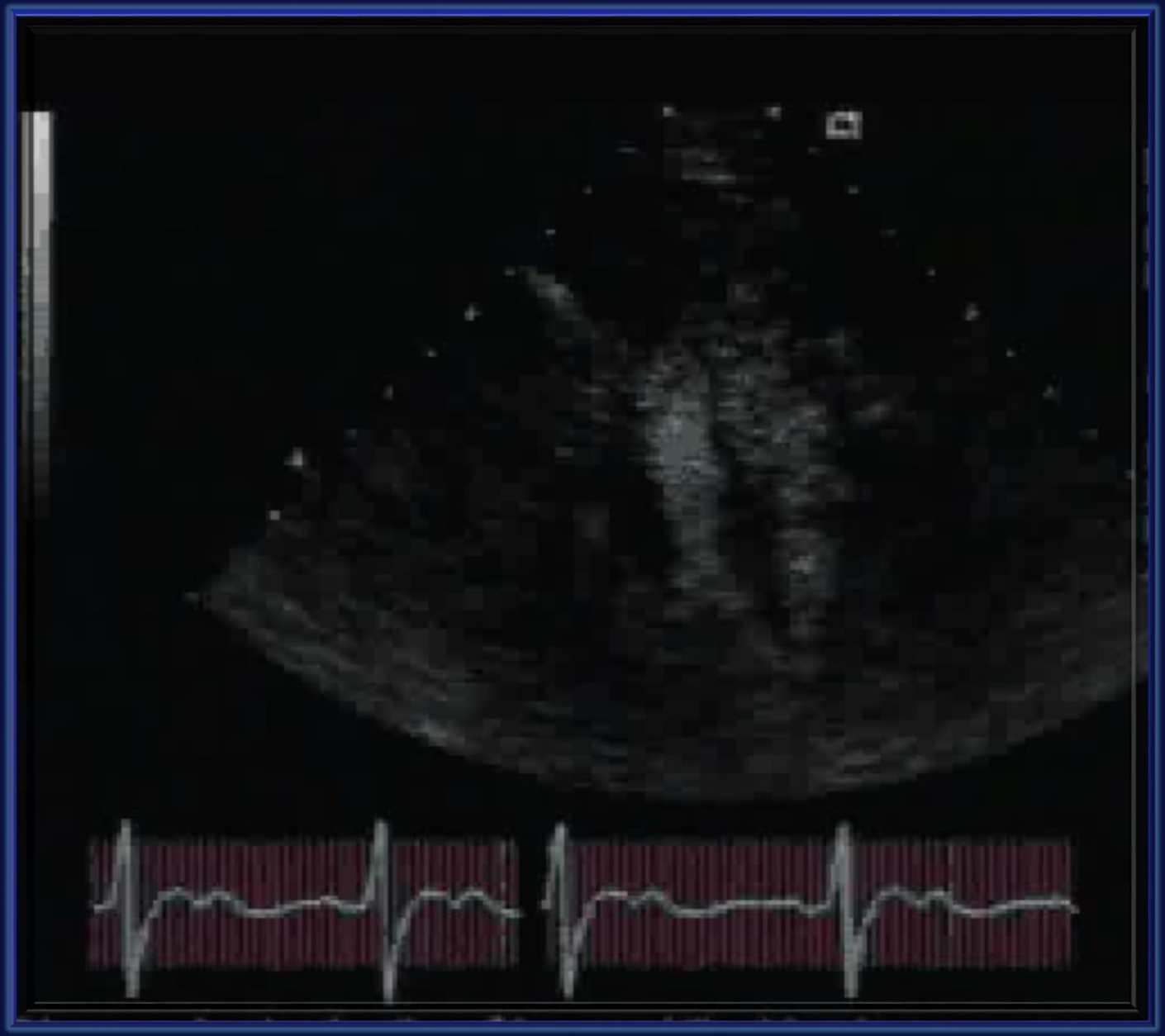
Lester SJ et al. J Am Soc Echocardiogr 2006 Jul; 19(7):919-23

Contrast Echocardiography

Structural Definition

1. LV Structural Abnormalities
   - Apical hypertrophy
   - Aneurysm / pseudoaneurysm
   - Thrombus
   - Noncompaction
   - Myocardial rupture

What's Up At The Apex?

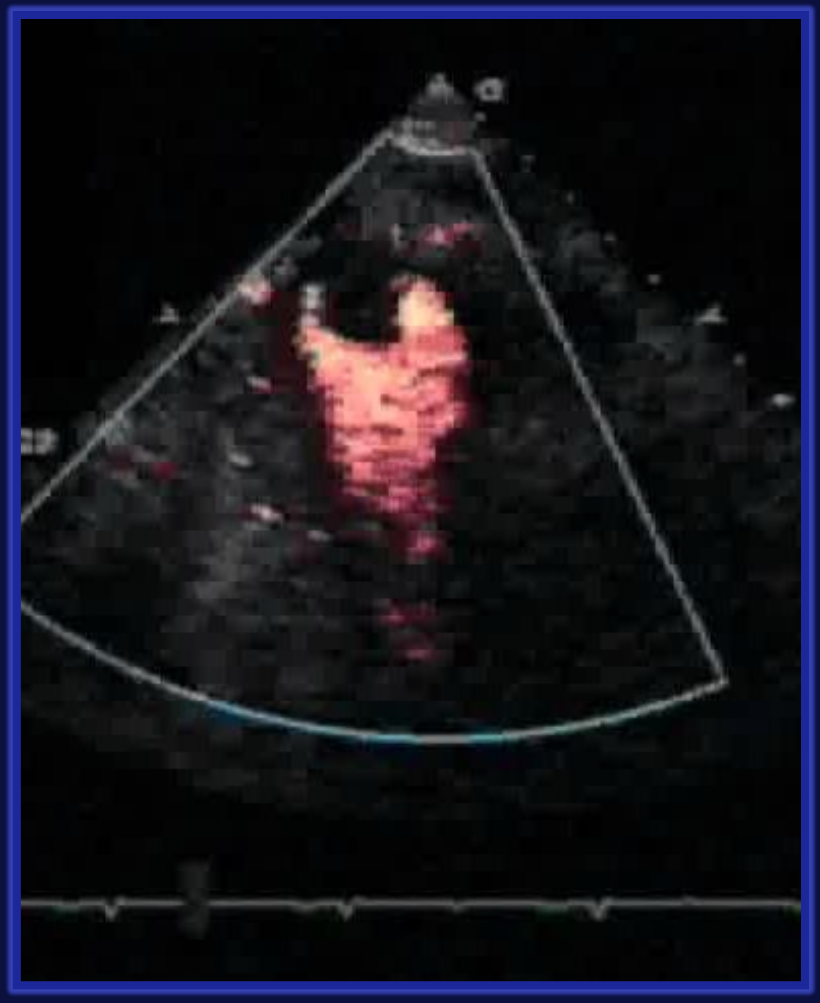


LV Structural Abnormalities

LV Aneurysm

LV Structural Abnormalities

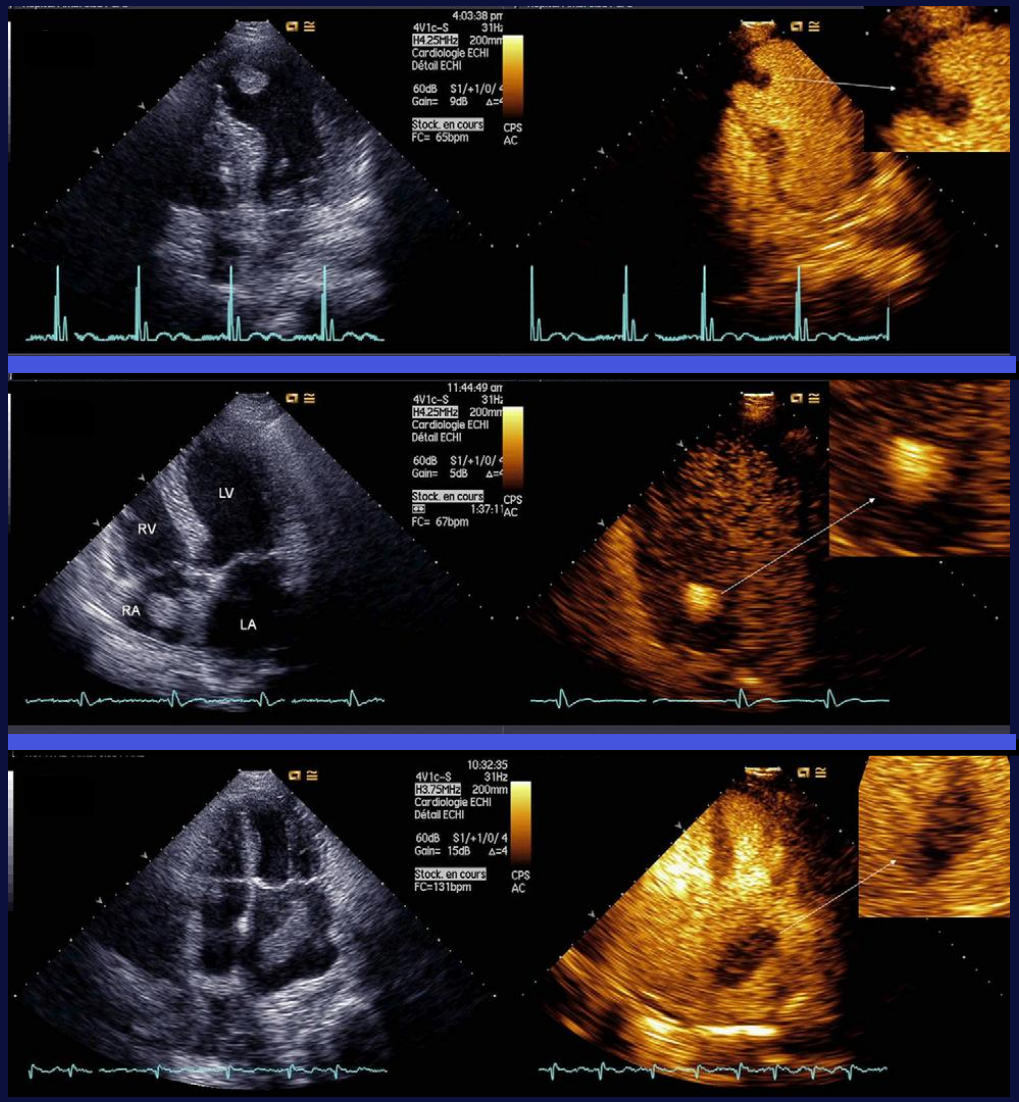
LV Aneurysm & More



Contrast Echocardiography
Structural Definition

1. **LV Structural Abnormalities**
   - Apical hypertrophy
   - Aneurysm / pseudoaneurysm
   - Thrombus
   - Noncompaction
   - Myocardial rupture
2. **Characterize intracardiac masses (tissue characterization)**

Characterize Intracardiac Masses



LV apical thrombus in patient post MI, no enhancement

Secondary cardiac tumor (renal sarcoma) located in RA, complete enhancement

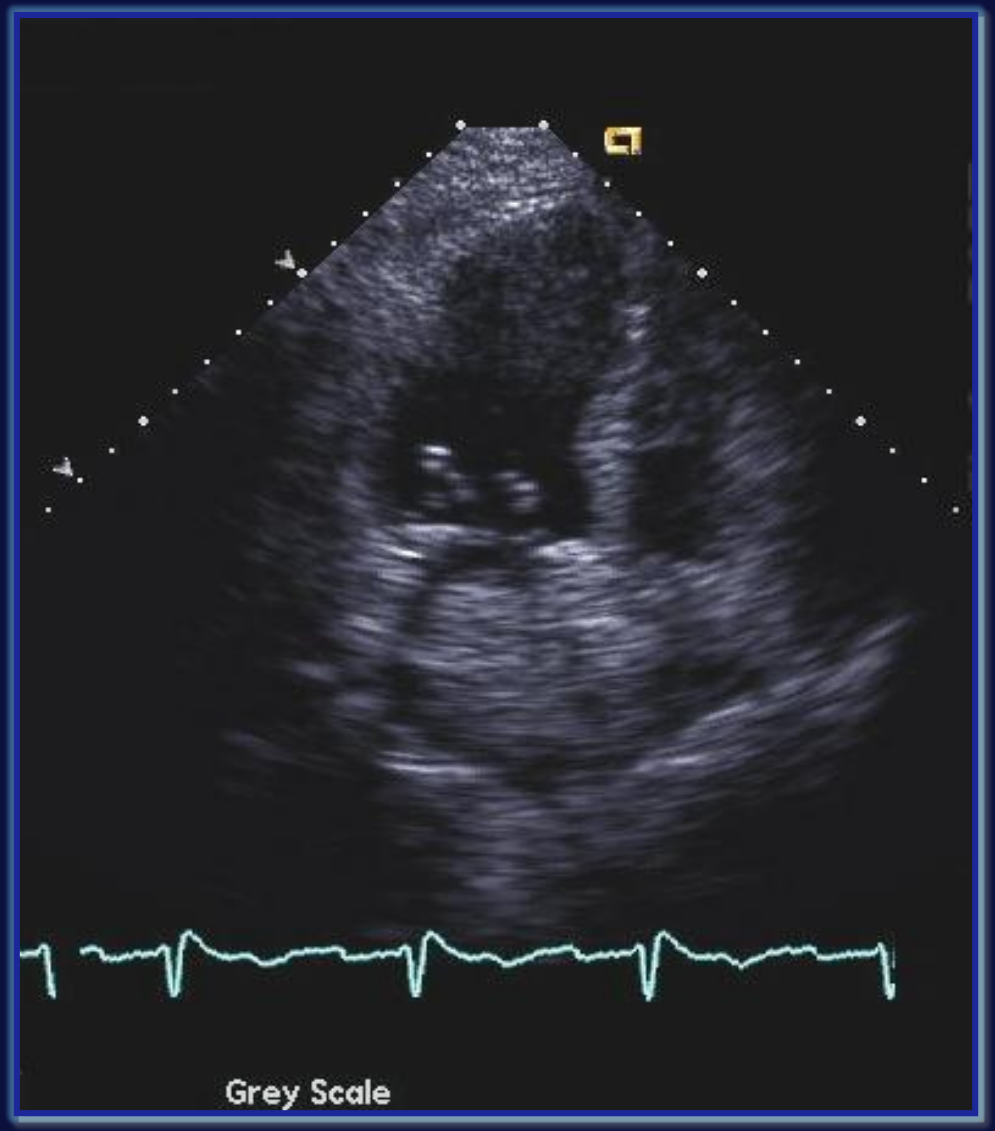
LA myxoma, partial enhancement

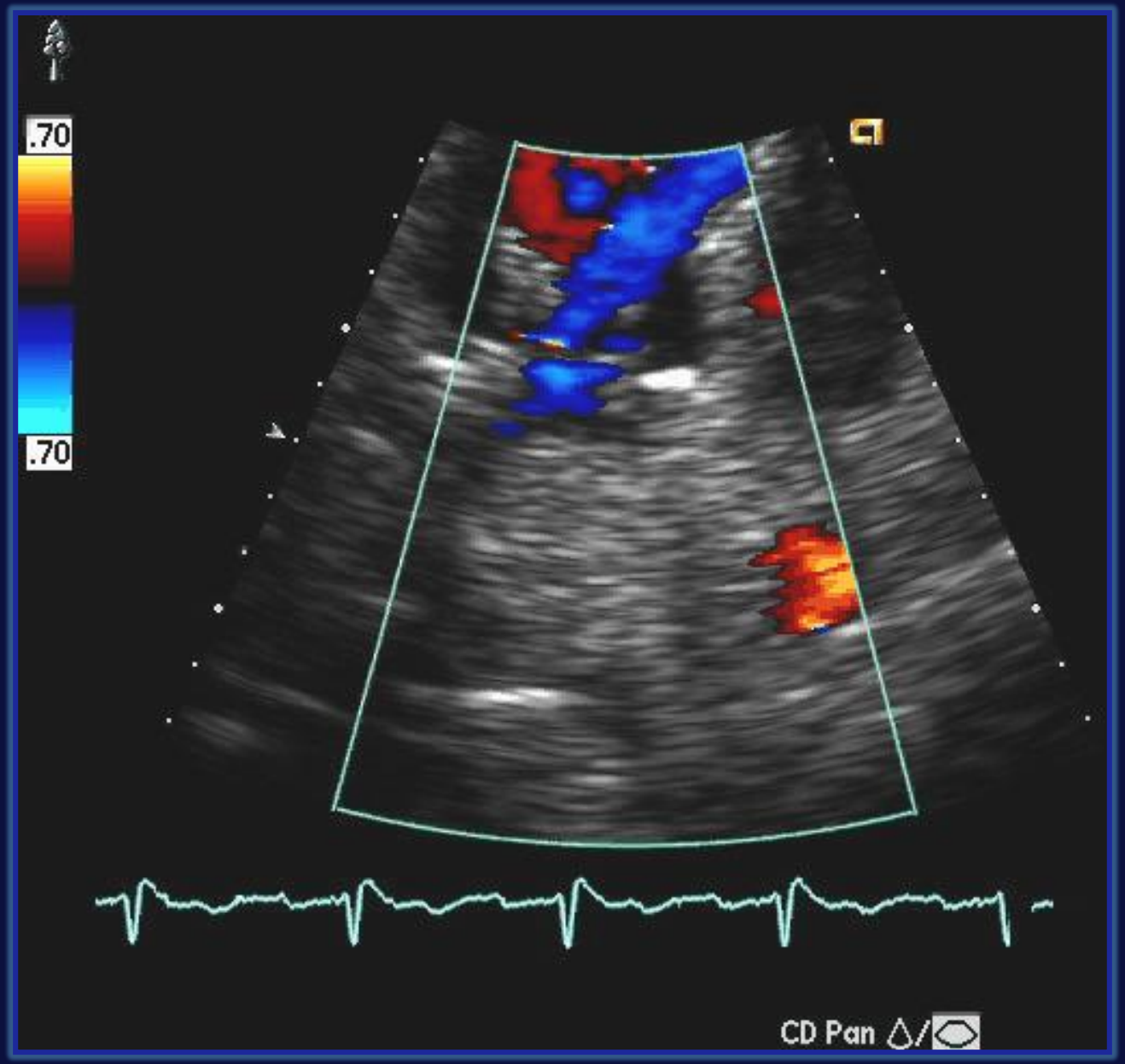
Mansencal et al. Archives of Cardiovascular Disease (2009) 102, 177—183

Contrast Echocardiography
Structural Definition

1. **LV Structural Abnormalities**
   - Apical hypertrophy
   - Aneurysm / pseudoaneurysm
   - Thrombus
   - Noncompaction
   - Myocardial rupture
2. **Characterize intracardiac masses (tissue characterization)**
3. **Differentiate artifacts**

Left Atrial Myxoma?

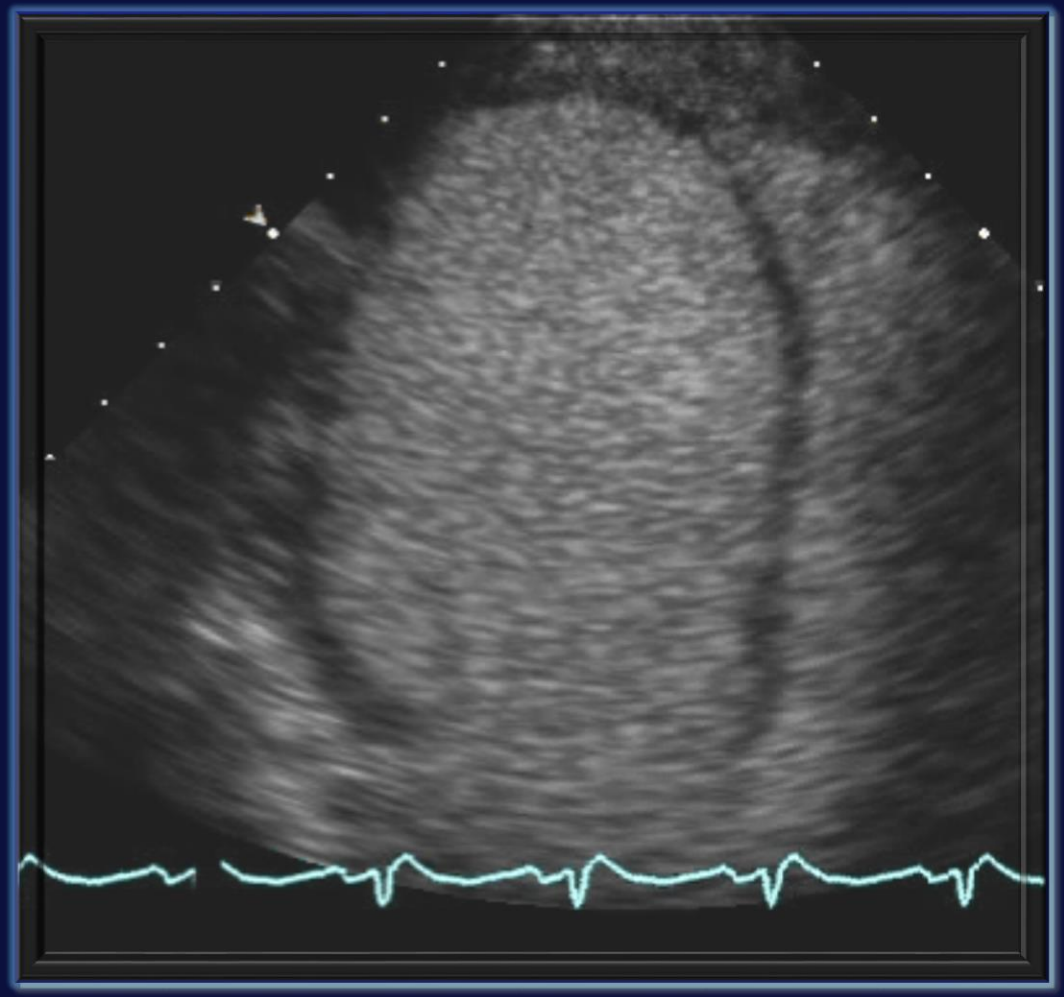



.70
.70
CD Pan

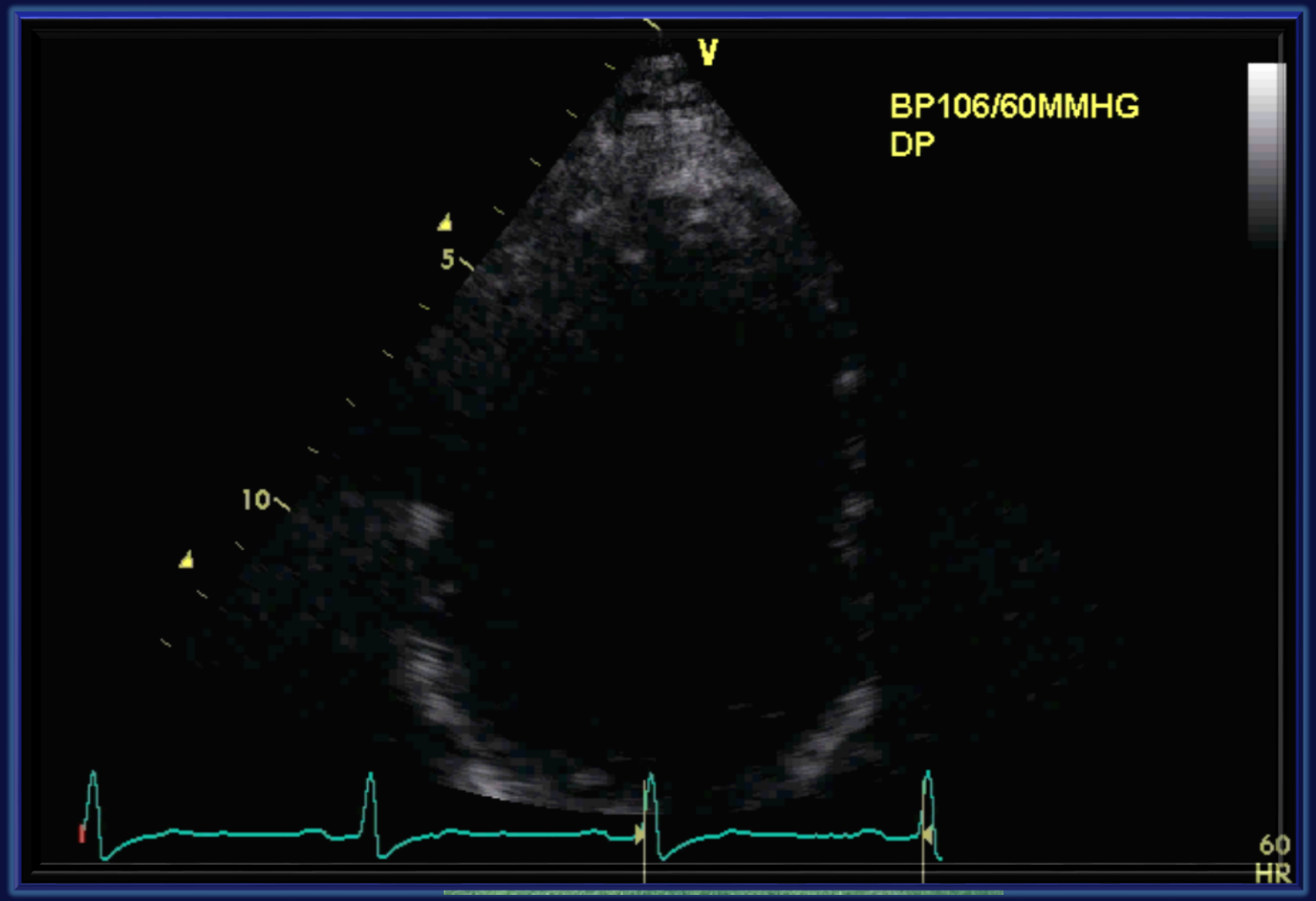

V
5
10
15
69
HR

Setup and System Settings

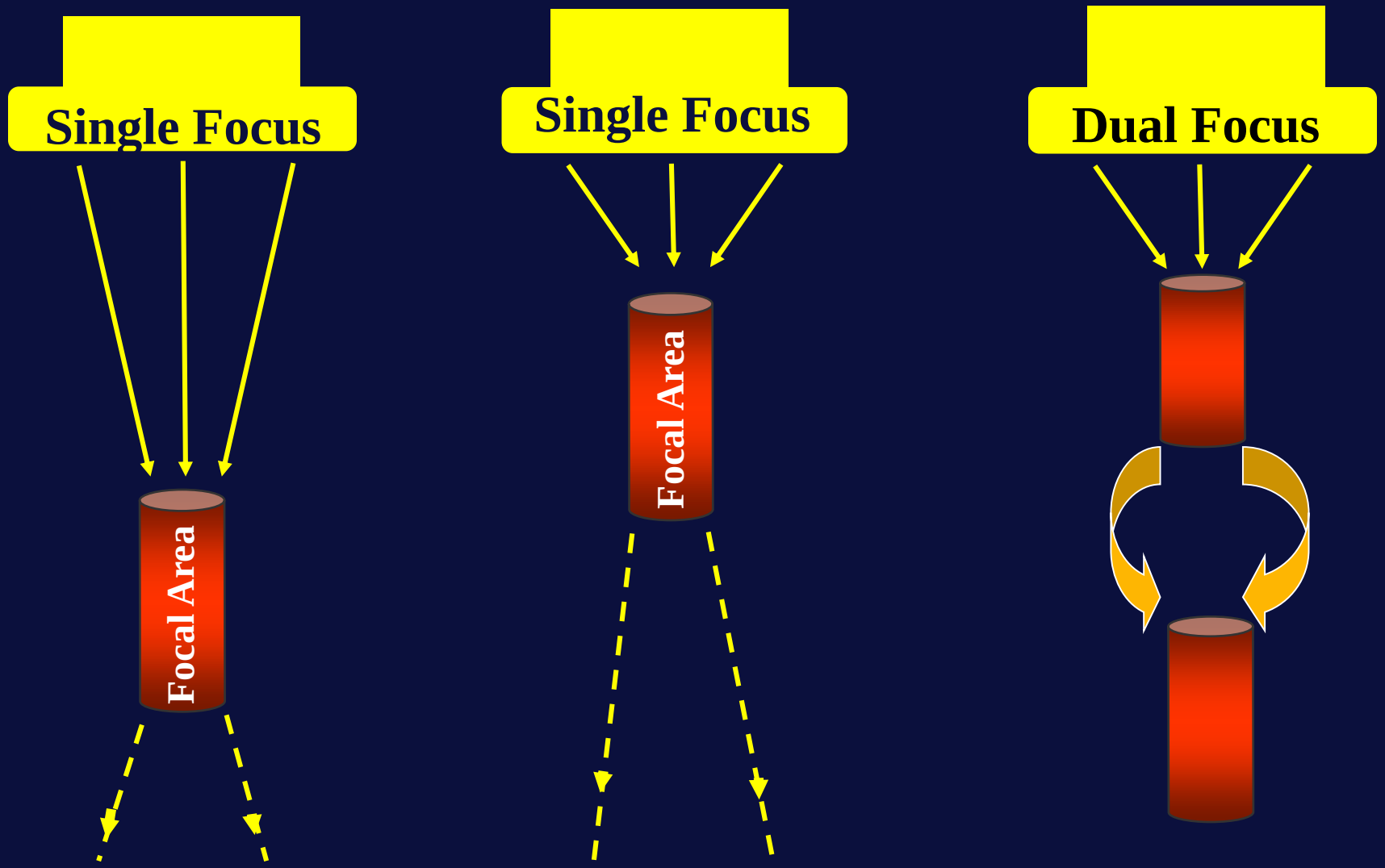
Machine and administration frequency adjusted to provide best image



Initial Image



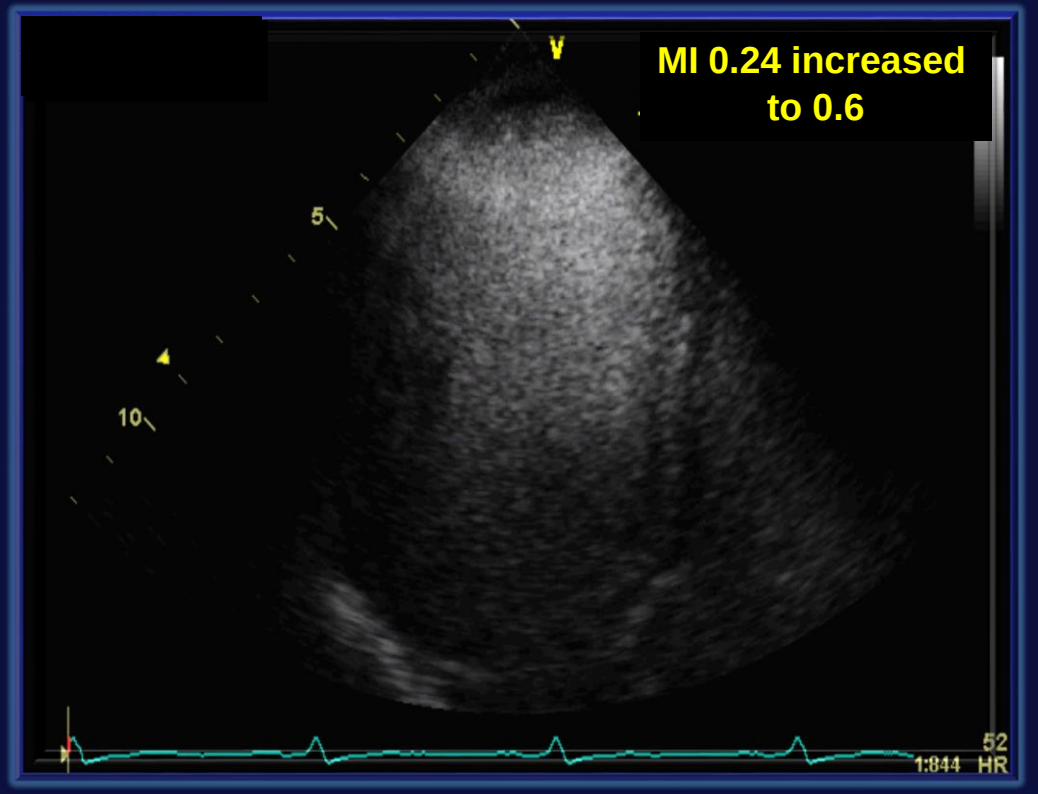
Focus



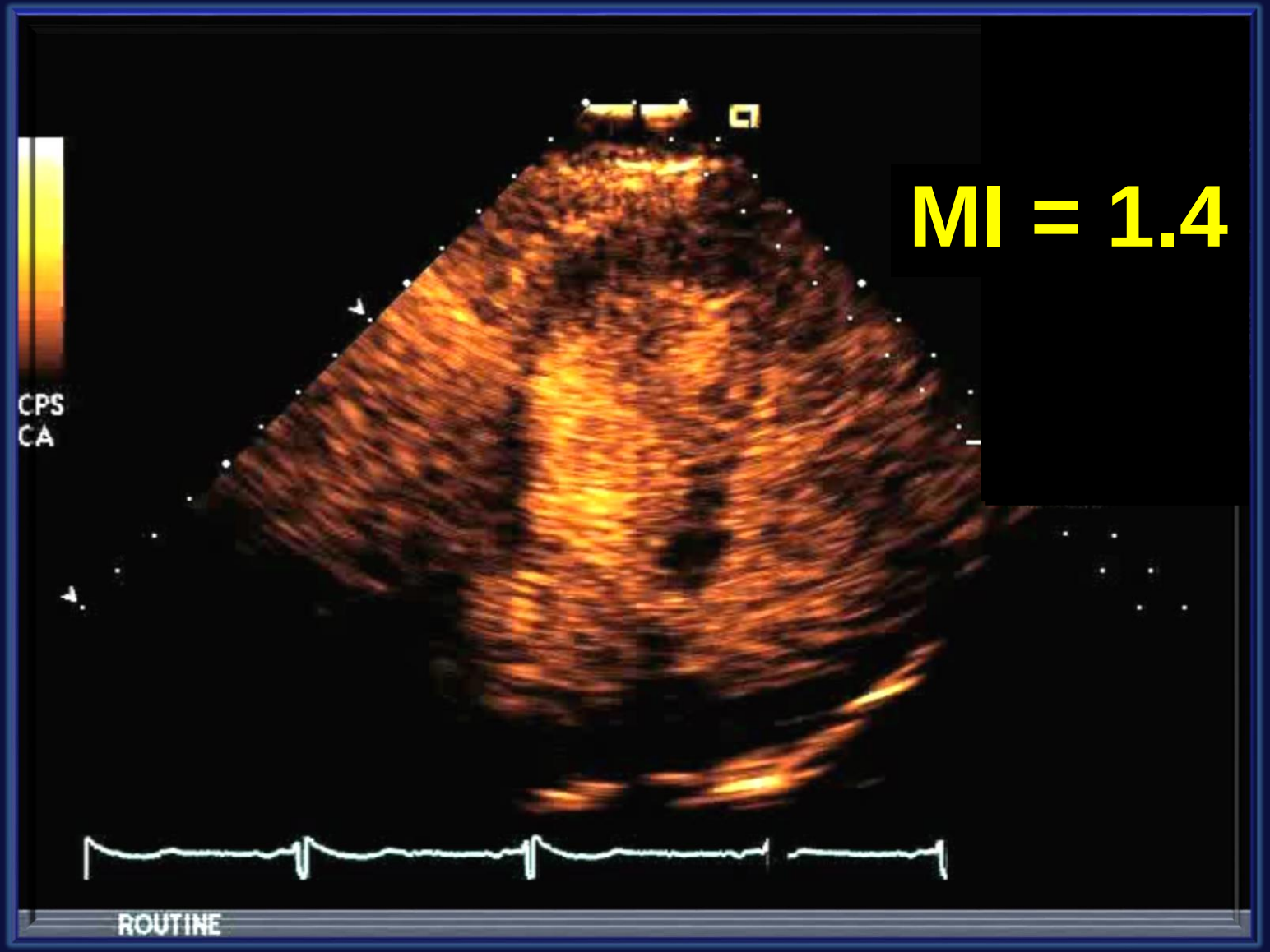
Impact of Mechanical Index

Mechanical Index

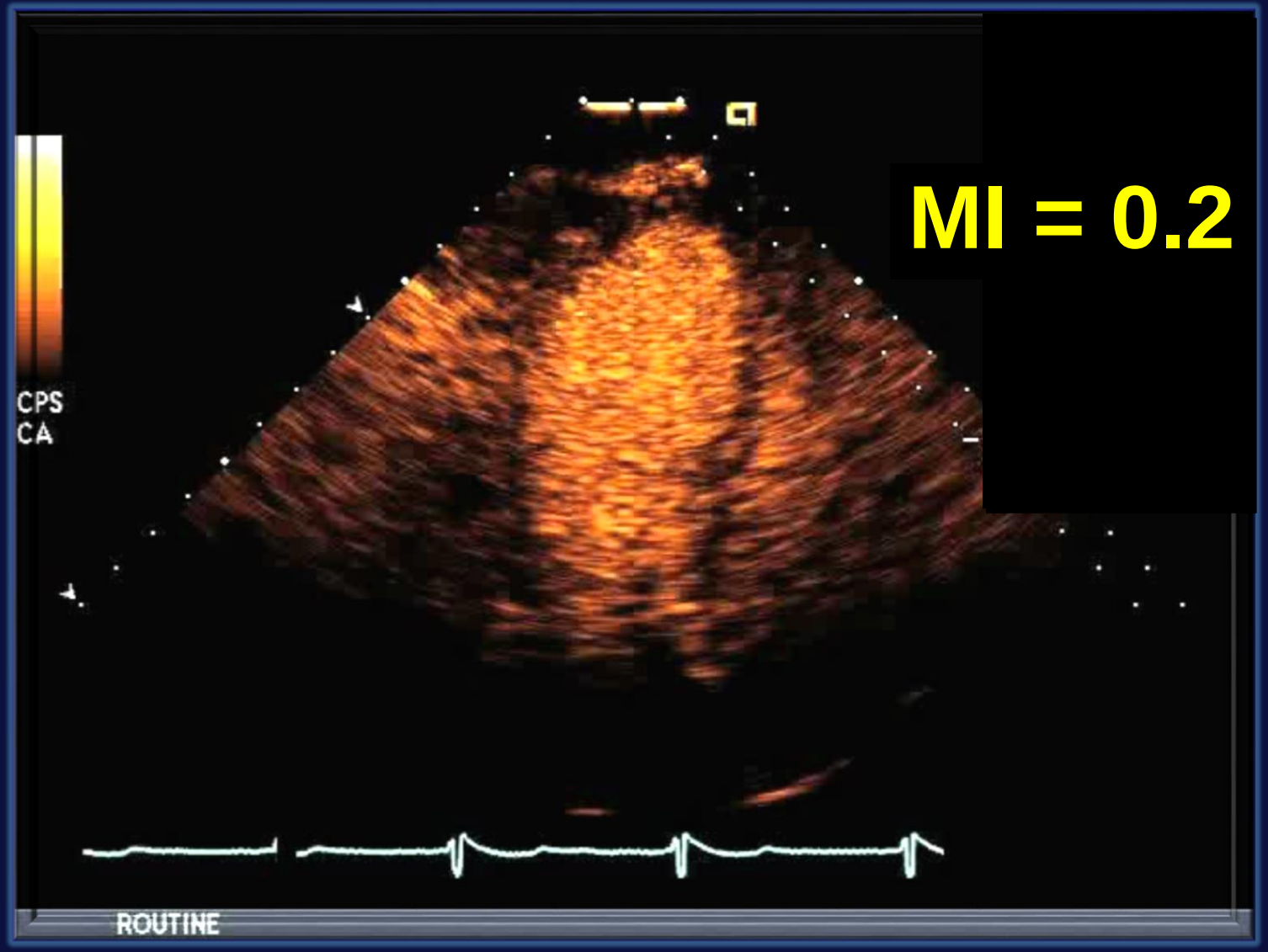
- Measure of output acoustic power
- High MI increases bubble destruction



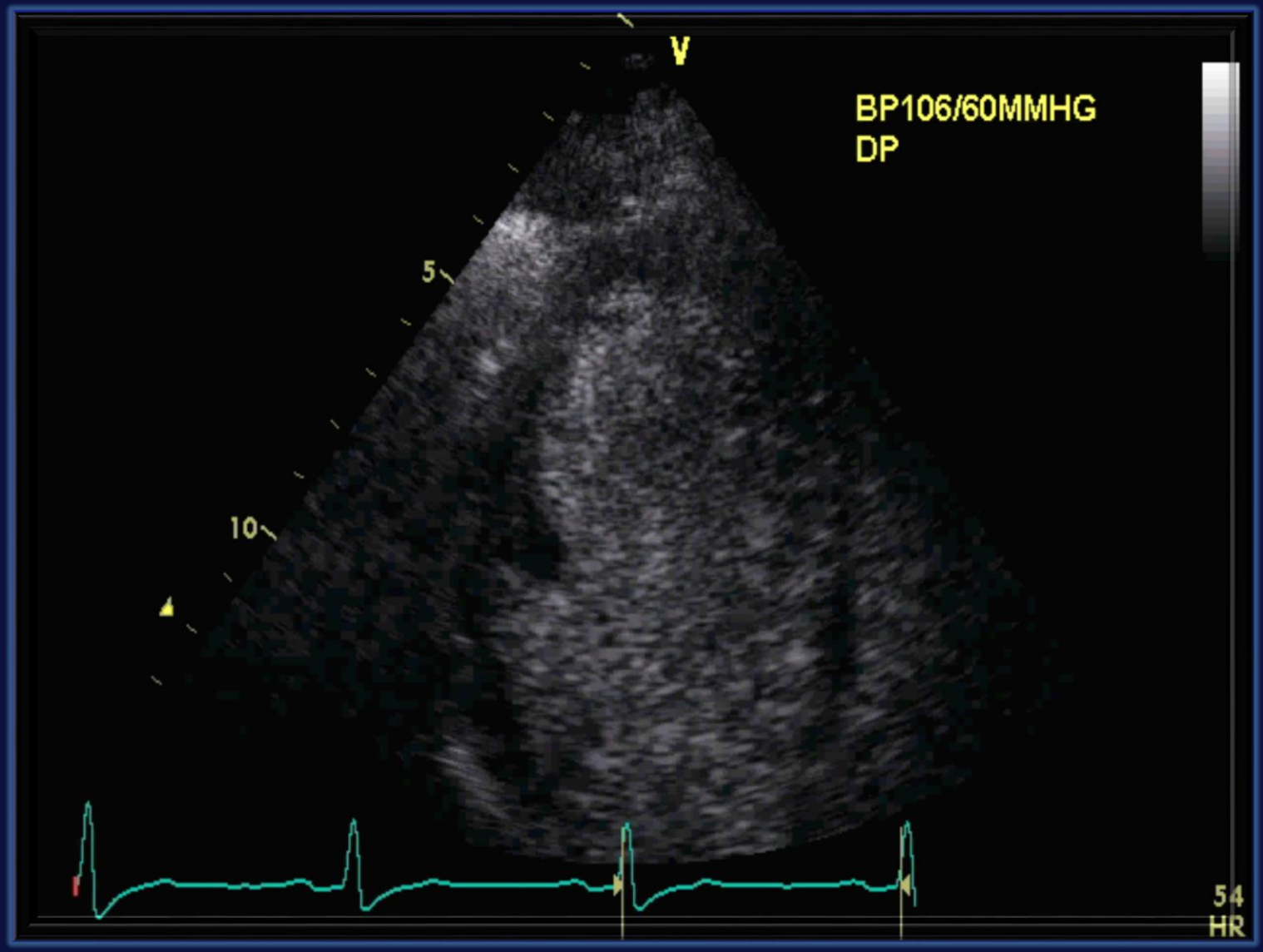
Suboptimal LV Opacification



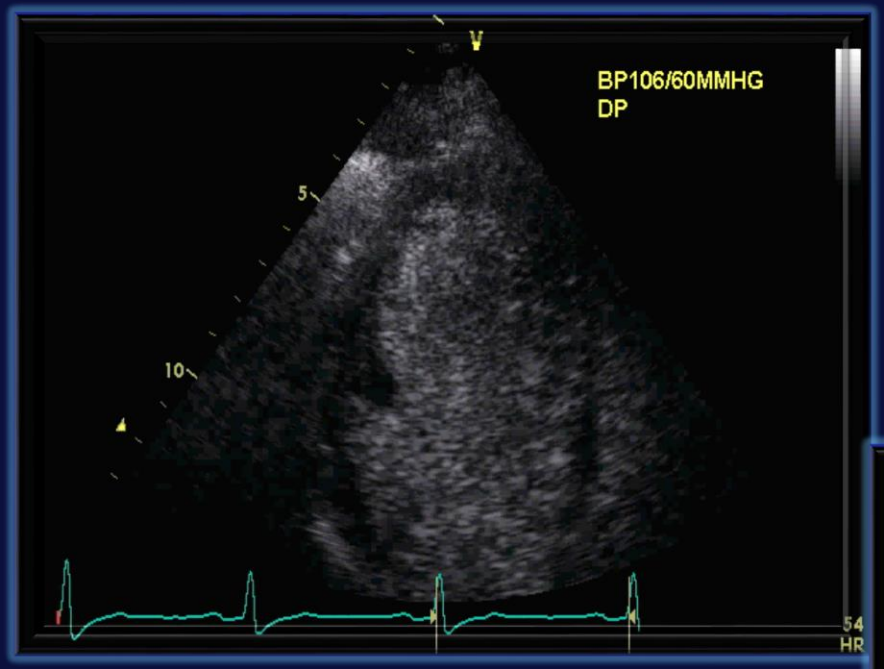
Optimal LV Opacification



Apical Dropout

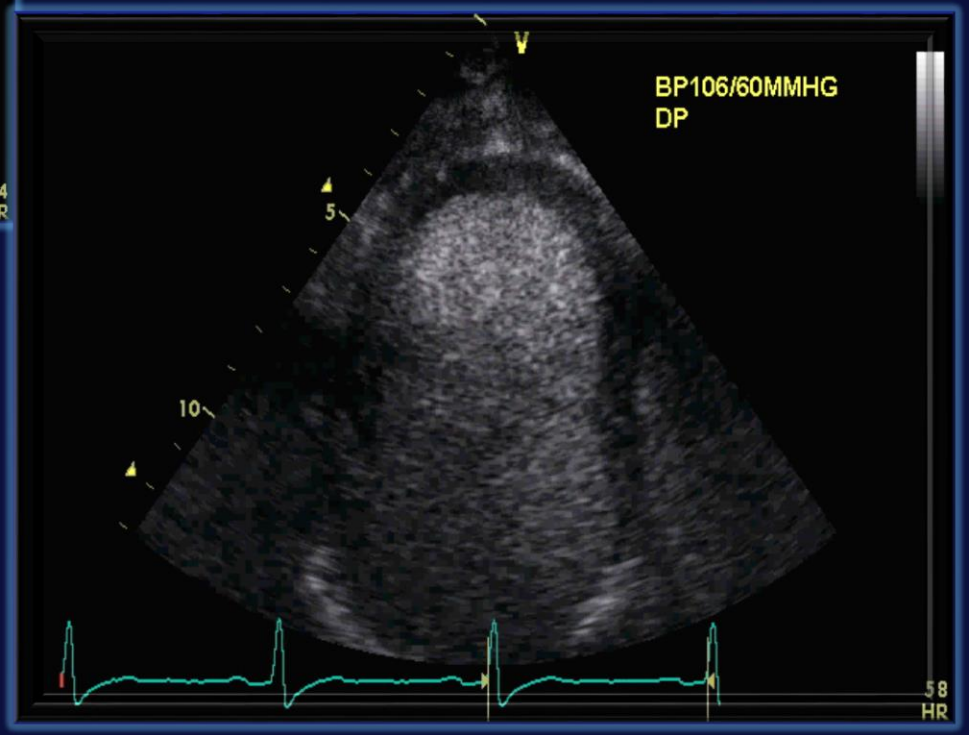


Apical Dropout



POTENTIAL CAUSES

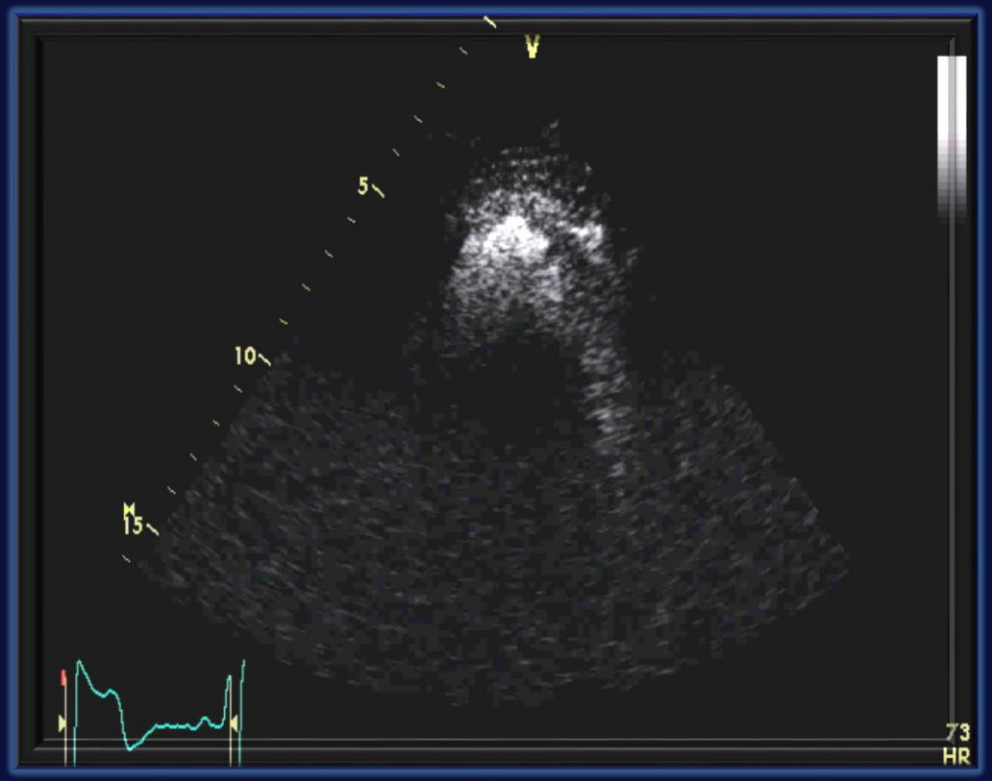
- System settings (*focal zone misplacement*)
- Dosing and administration (*low concentration*)



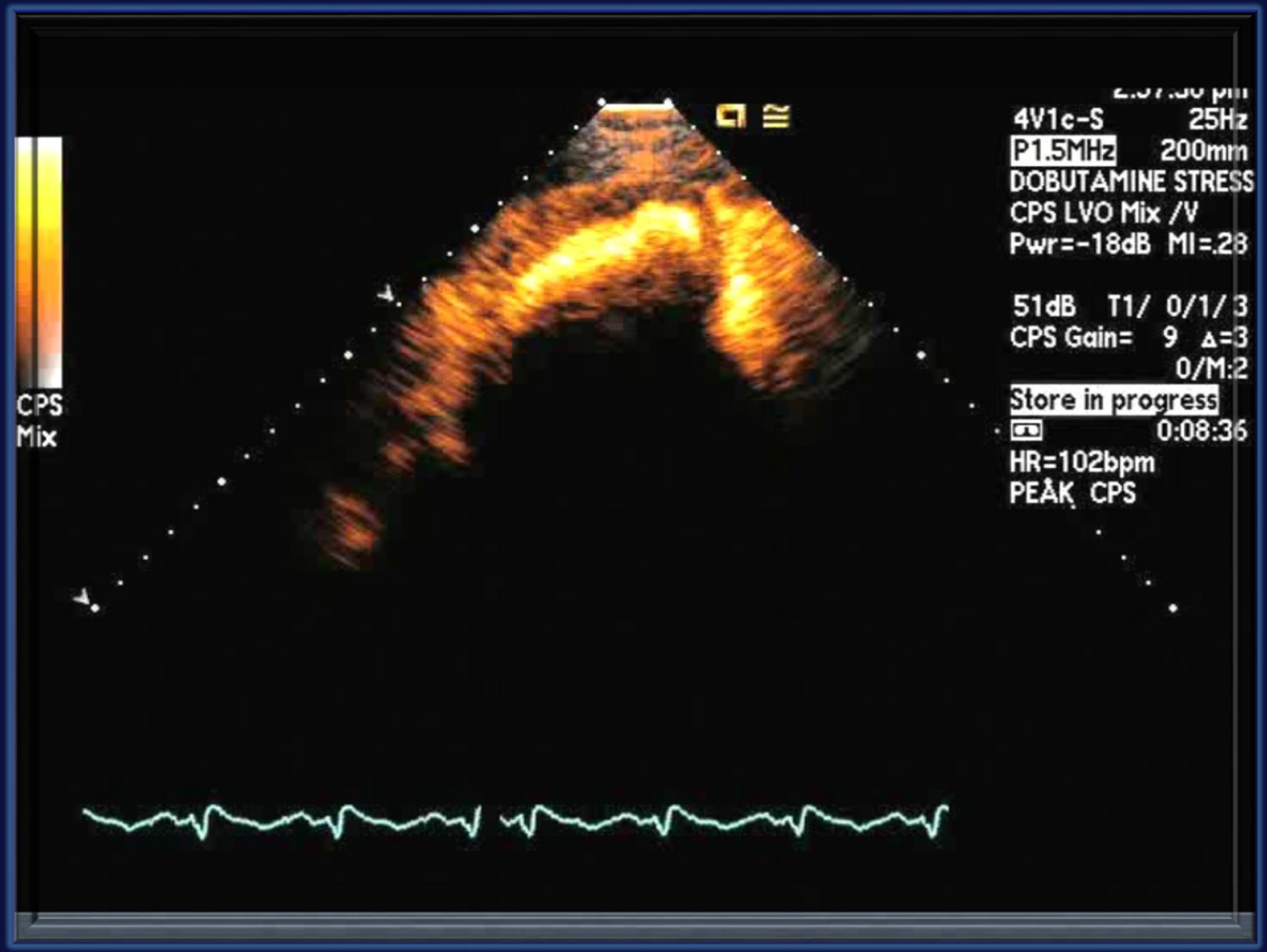
Attenuation

POTENTIAL CAUSES

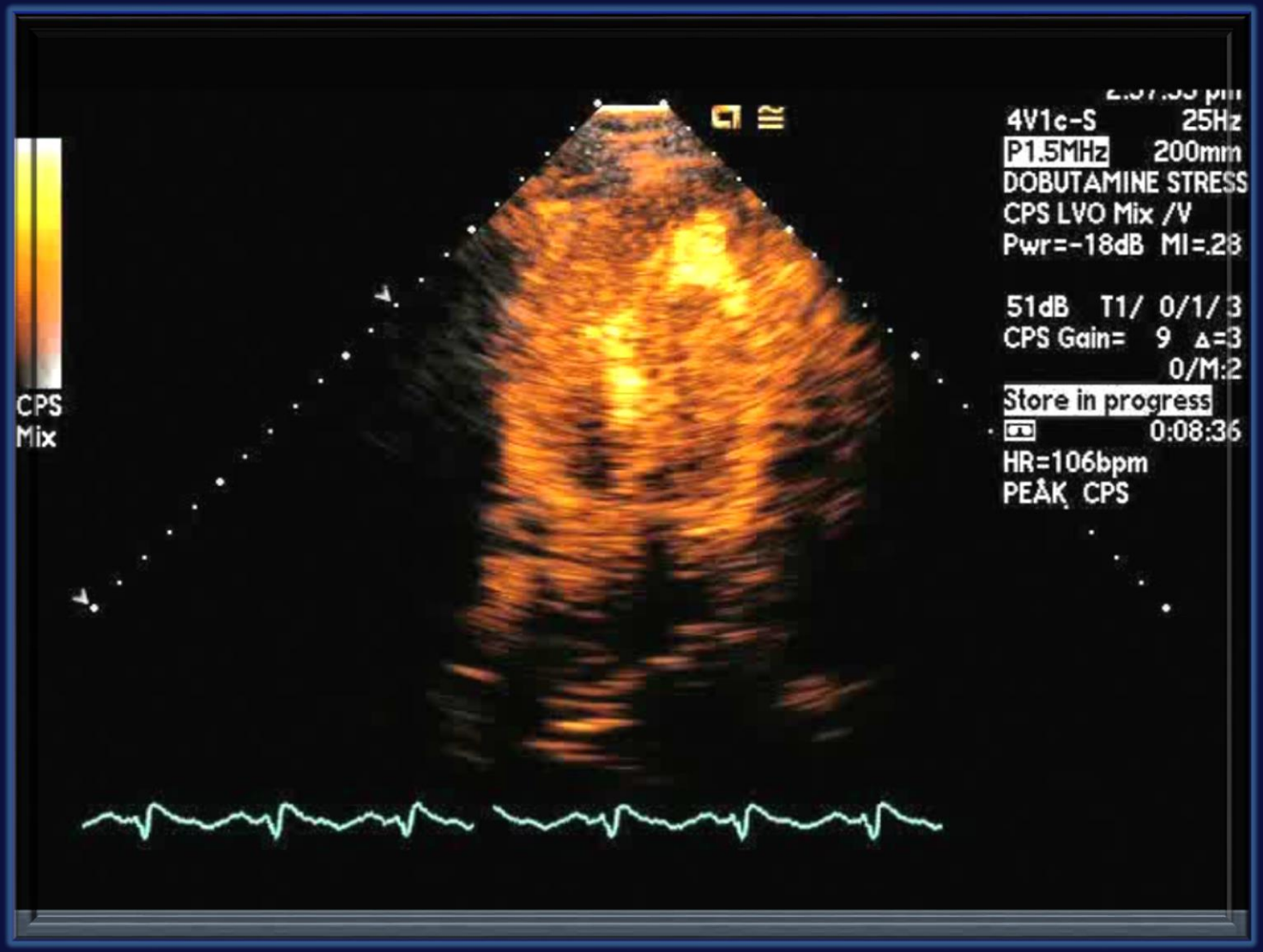
- **Dosing (*high concentration*)**
- **Administration (*infusion rate too fast*)**
- **Clinician (*obtain off-axis windows*)**



Tincture of Time



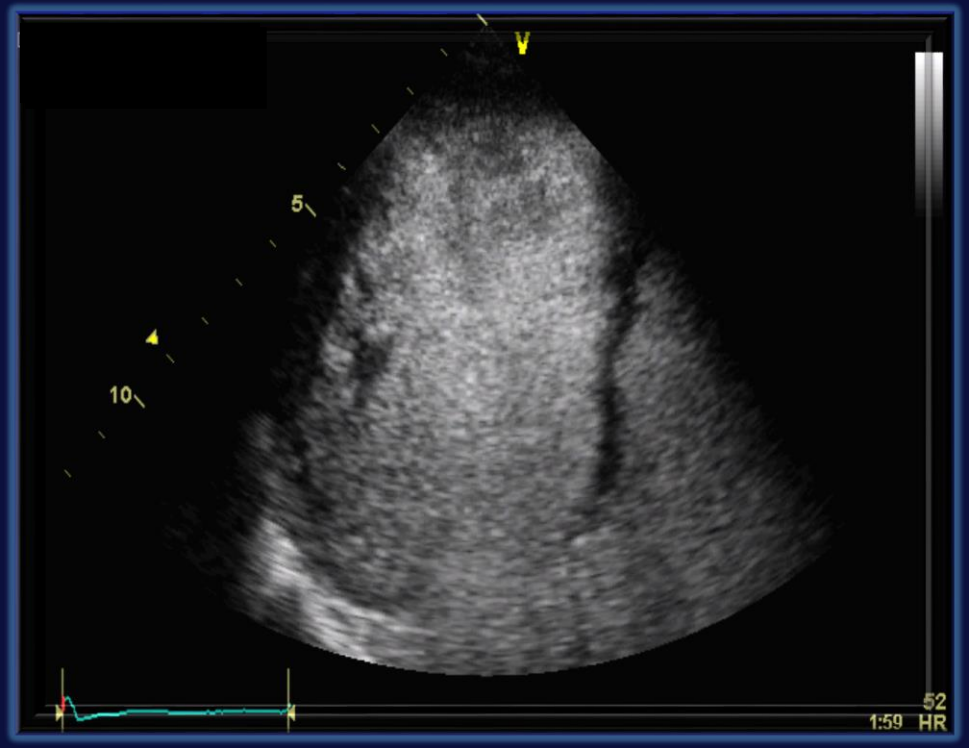
Burst Some Bubbles: Flash



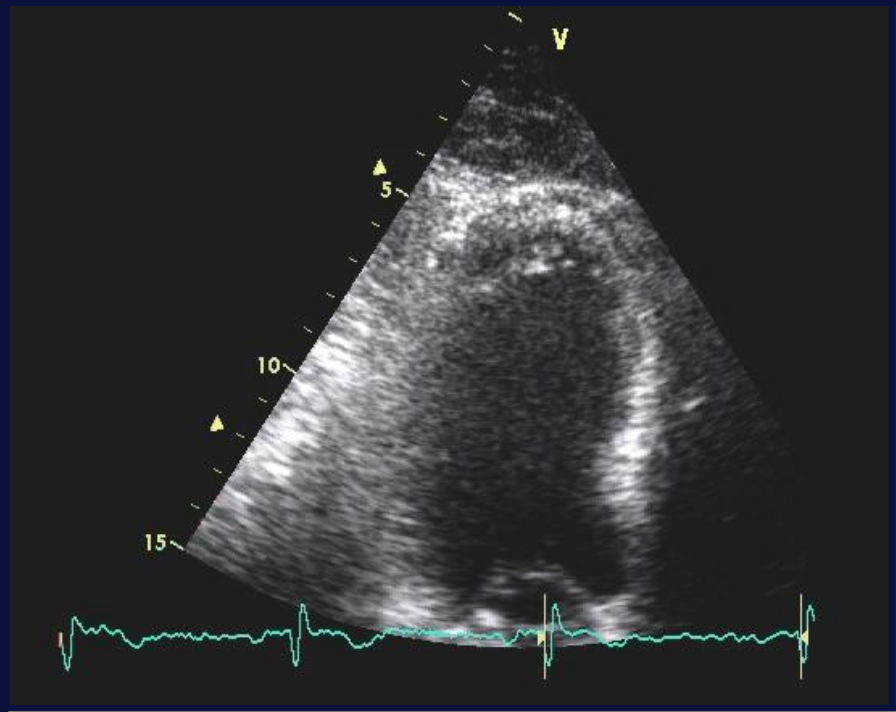
Swirling

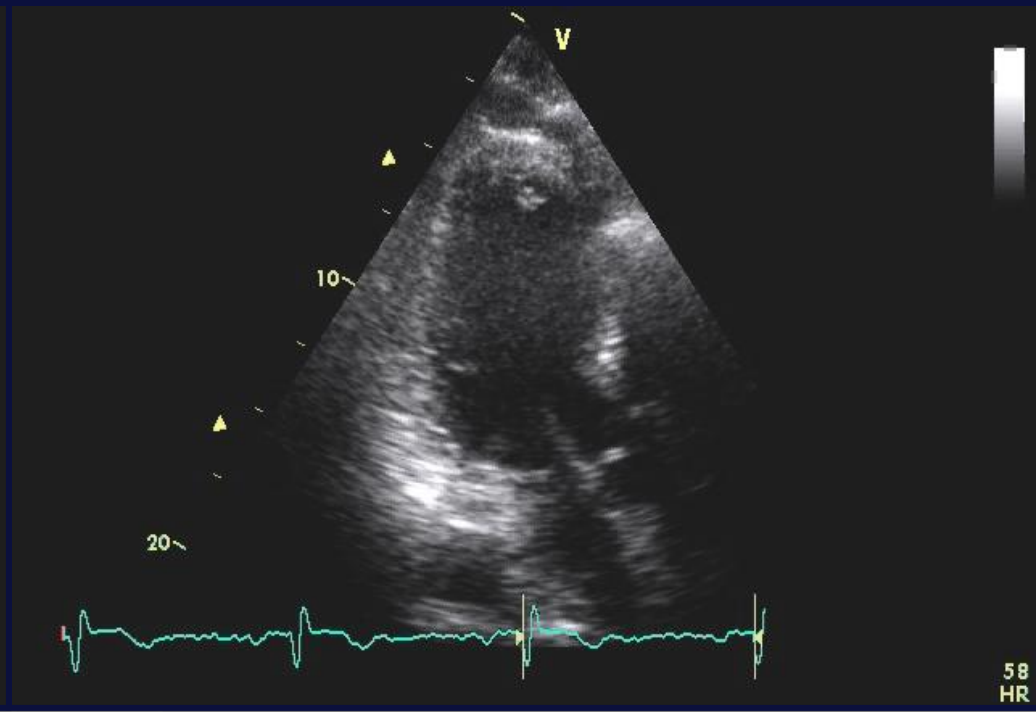
POTENTIAL CAUSES

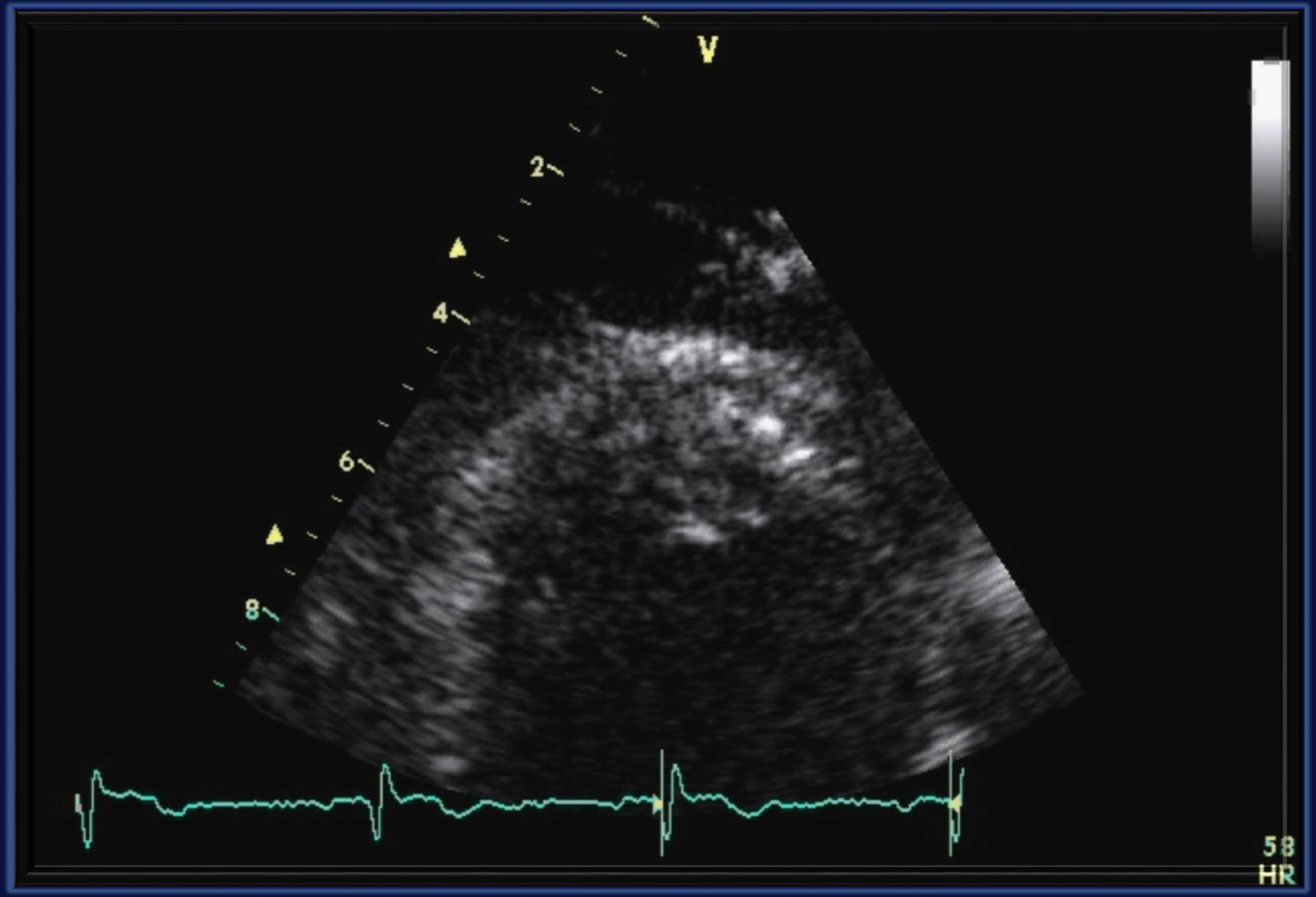
- System settings (*high MI*)
- Dosing (*low concentration*)
- Administration (*low infusion rate*)
- Poor LV function



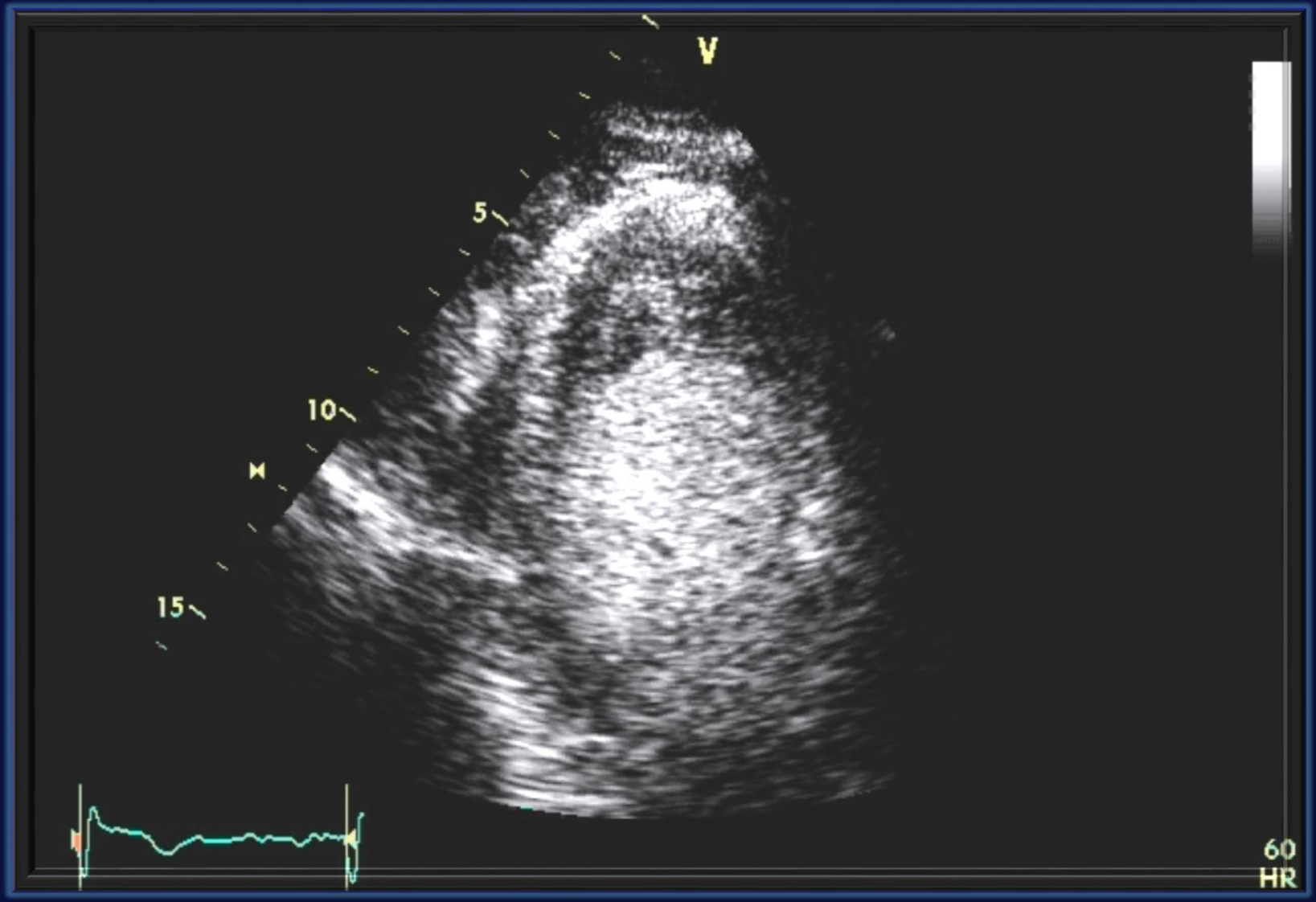
Thrombus?



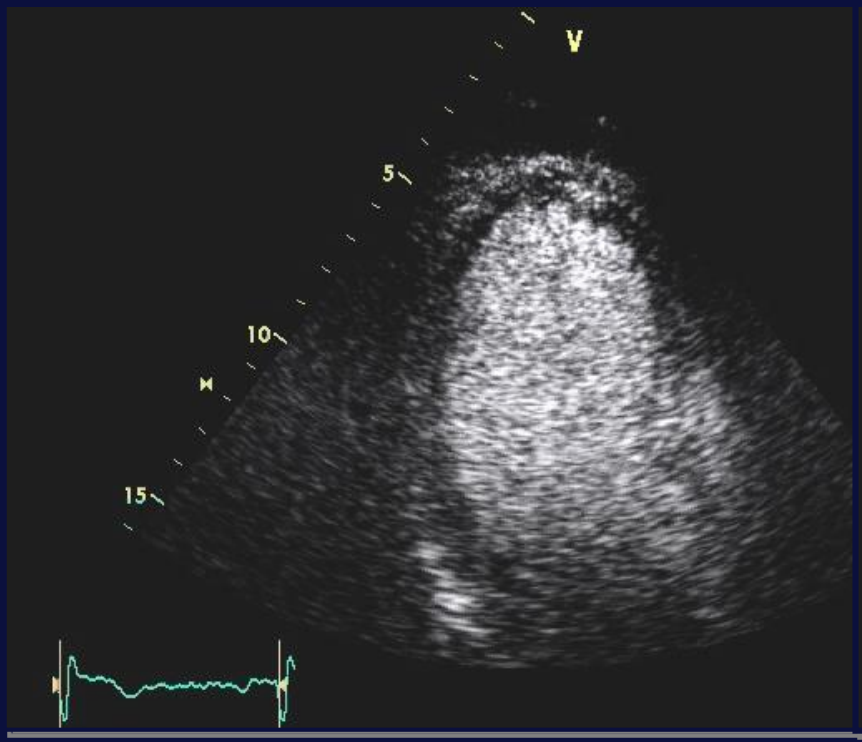


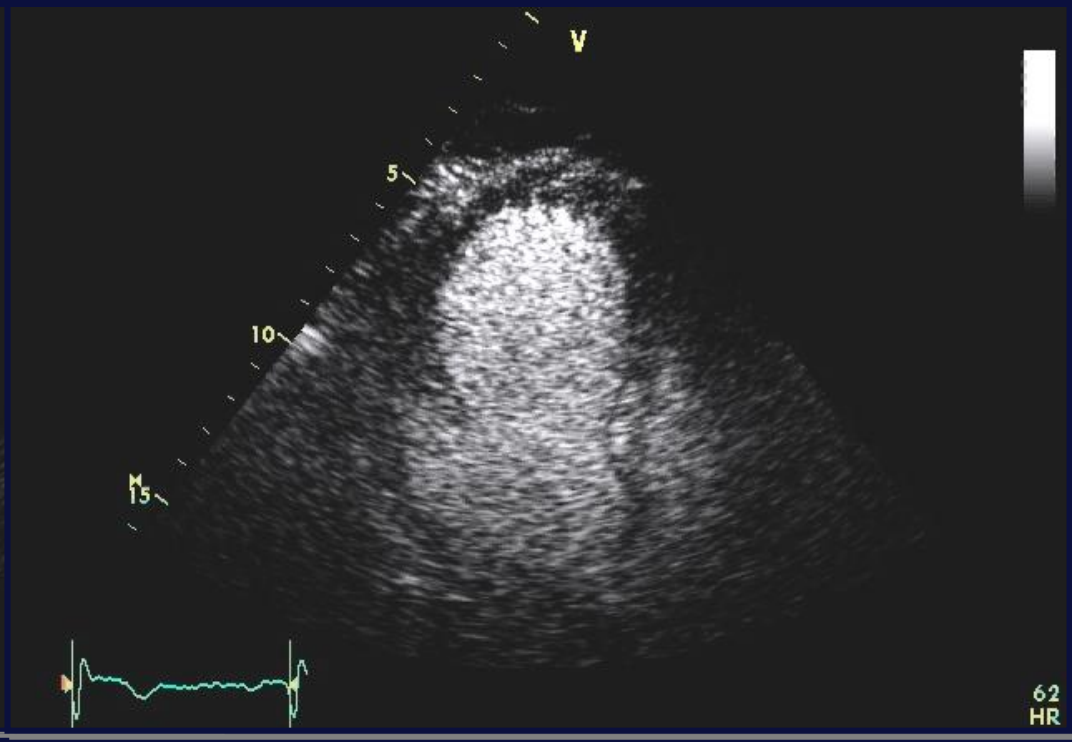

V
2
4
6
8
58
HR

Did Contrast Help?



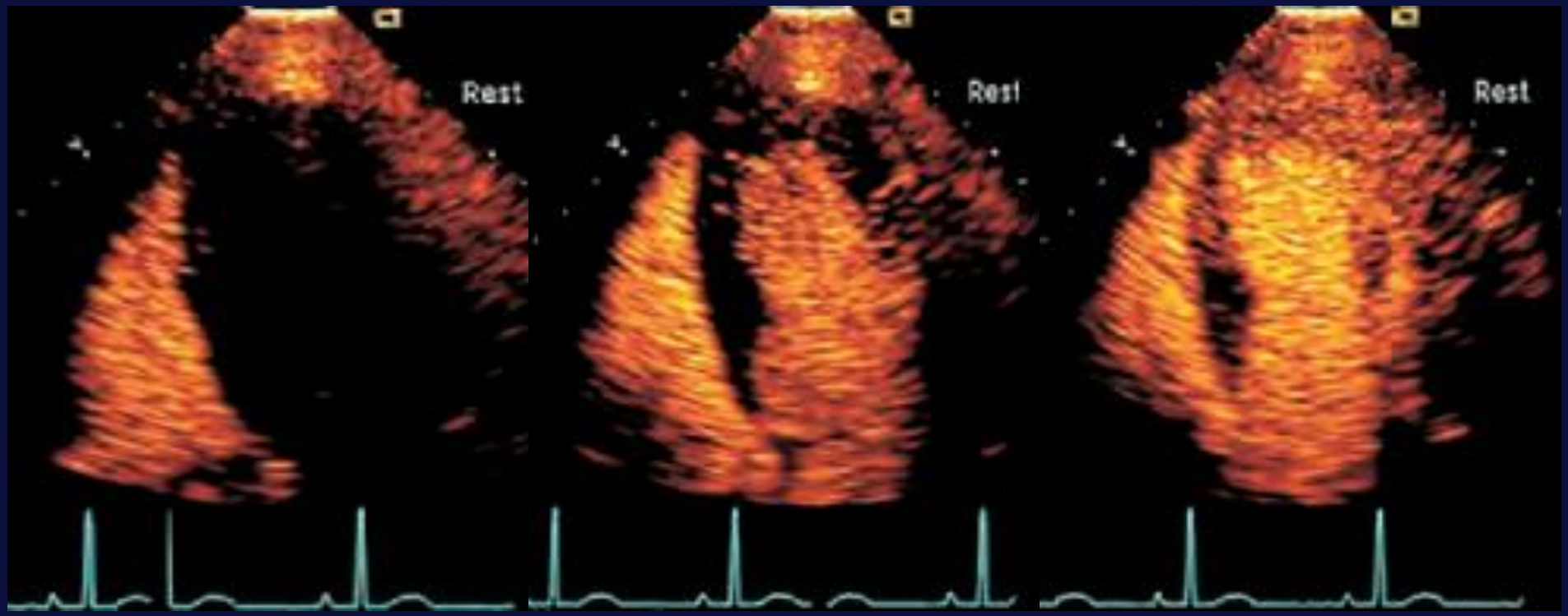
Instrument Set Up





Myocardial Contrast Echocardiography
Perfusion

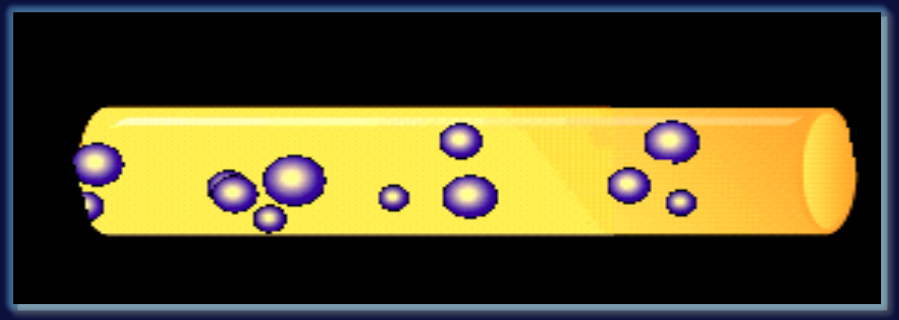
Right Ventricle | LVO Phase | Myocardial Phase



J Am Soc Echocardiogr 2008

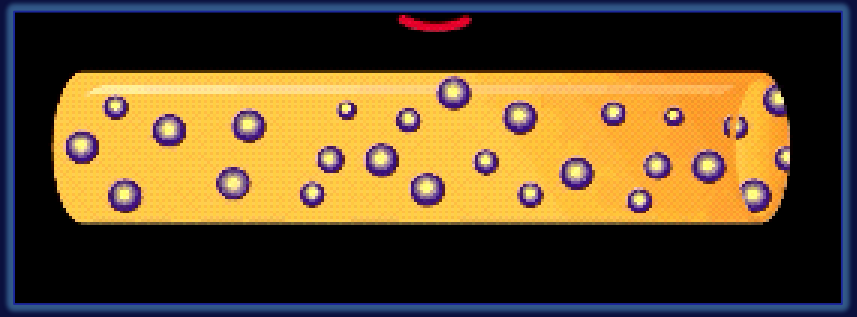
Myocardial Contrast Echocardiography
Perfusion

Low MI, Nondestructive
Real Time



Continuous Imaging

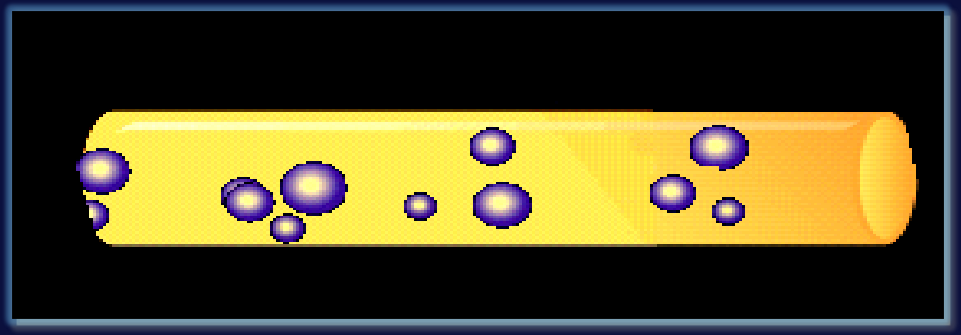
High MI, Destructive
Triggered



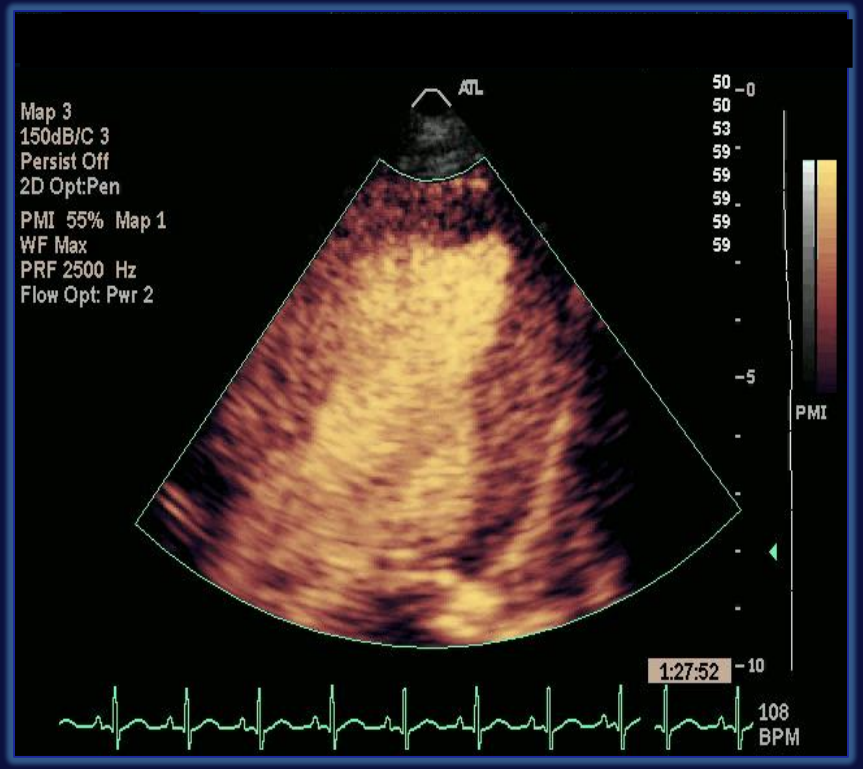
Intermittent Imaging

Myocardial Contrast Echocardiography
Perfusion

Low MI, Nondestructive
Real Time

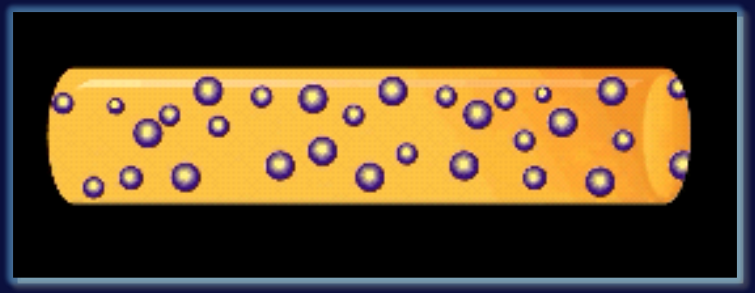


Continuous Imaging

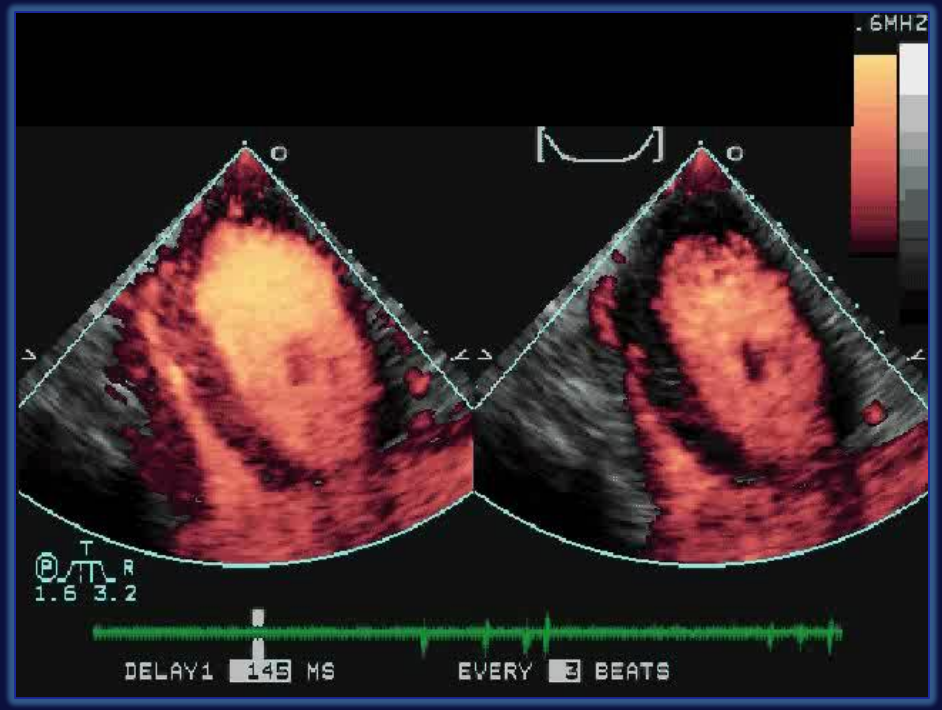


Myocardial Contrast Echocardiography
Perfusion

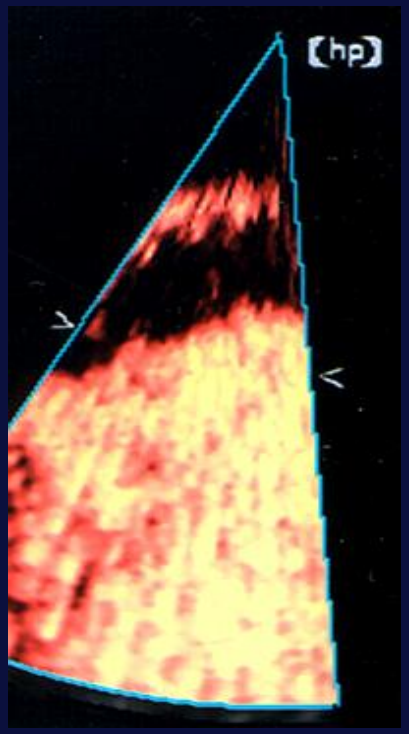
High MI, Destructive Triggered



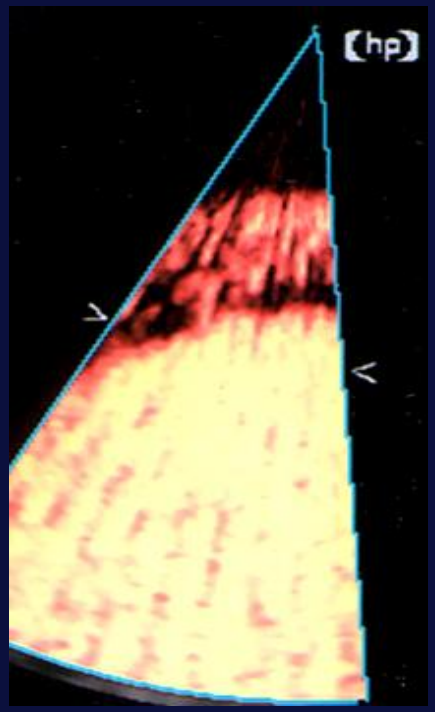
Intermittent Imaging



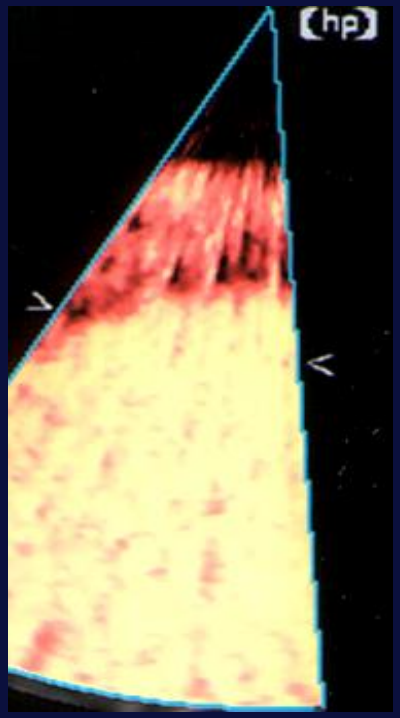
Triggering



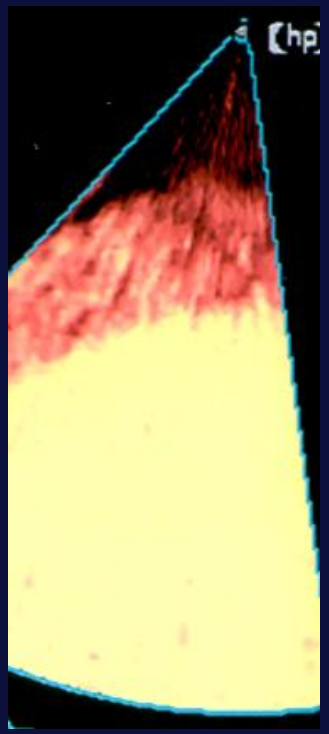
1 beat



5 beats

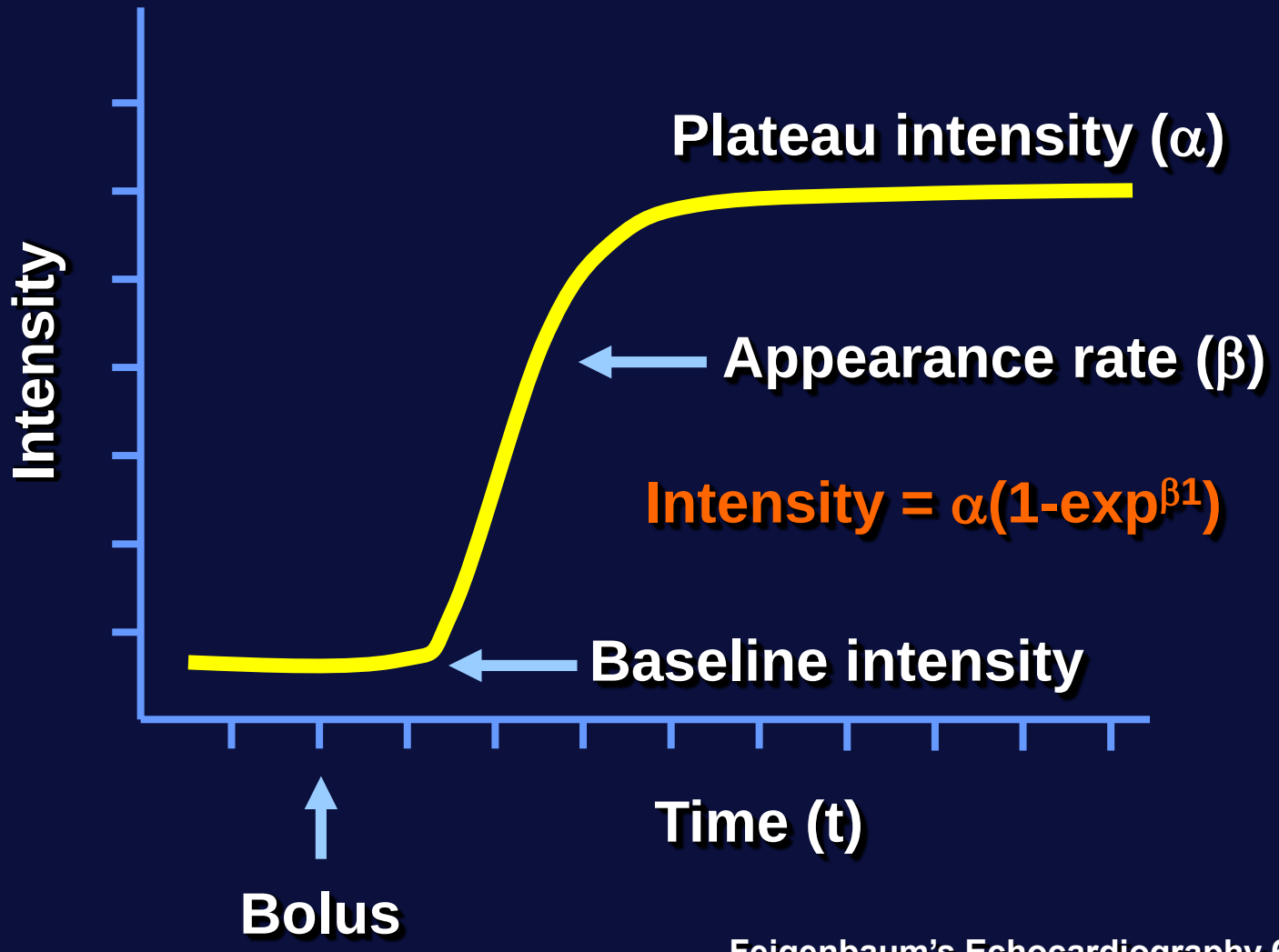


32 beats



44 beats

Time Of Appearance Curve



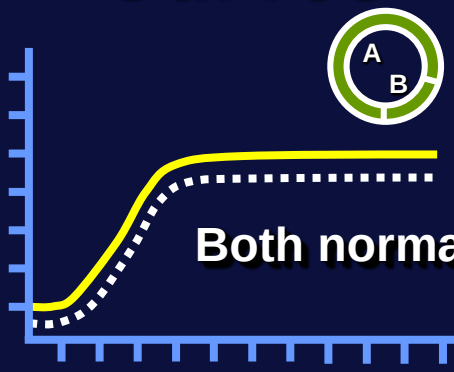
Feigenbaum's Echocardiography 6th edition

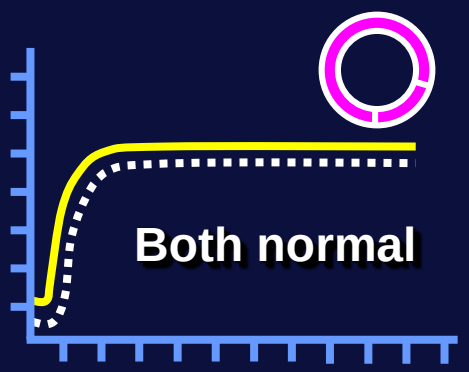
Baseline Curves

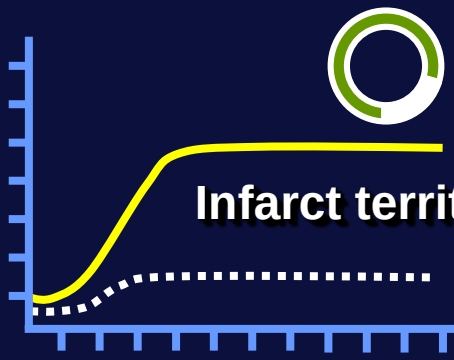
Vasodilator Curves

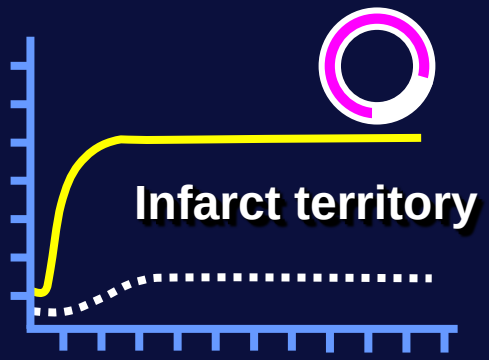
— A: normal reference area

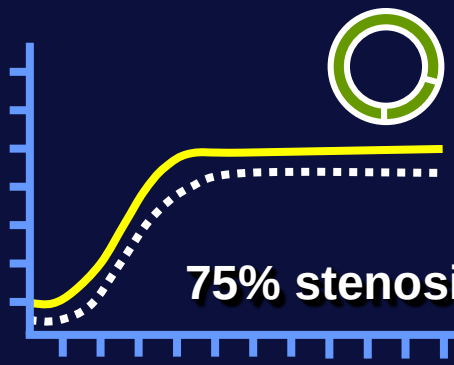
···· B: area of coronary obstruction

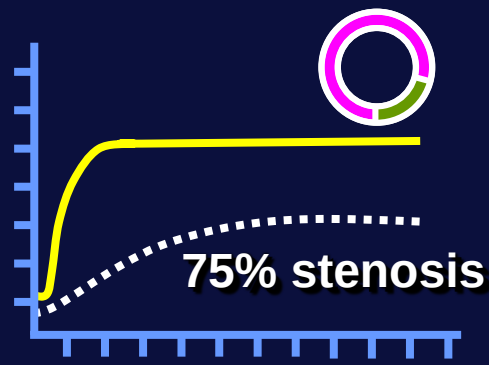








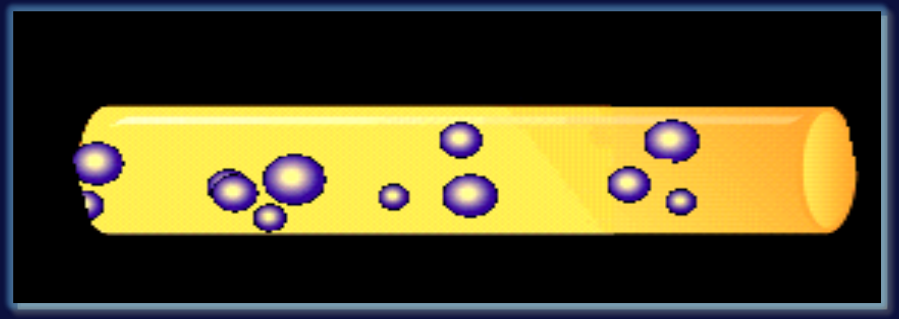




Feigenbaum's Echocardiography 6th edition

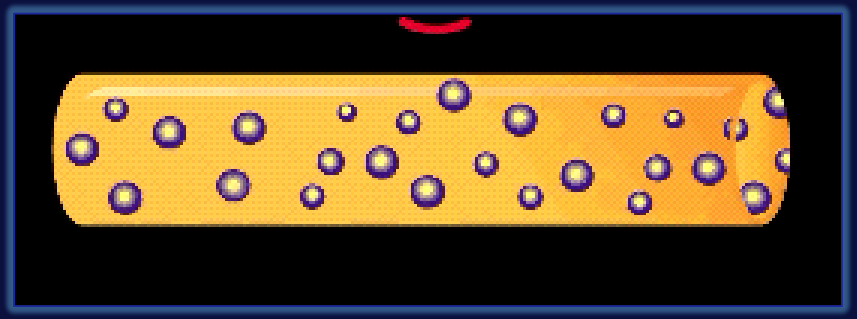
Myocardial Contrast Echocardiography
Perfusion

Low MI, Nondestructive
Real Time



Continuous Imaging

High MI, Destructive
Triggered



Intermittent Imaging

Safety of Echocardiographic Contrast Agents?

Warning

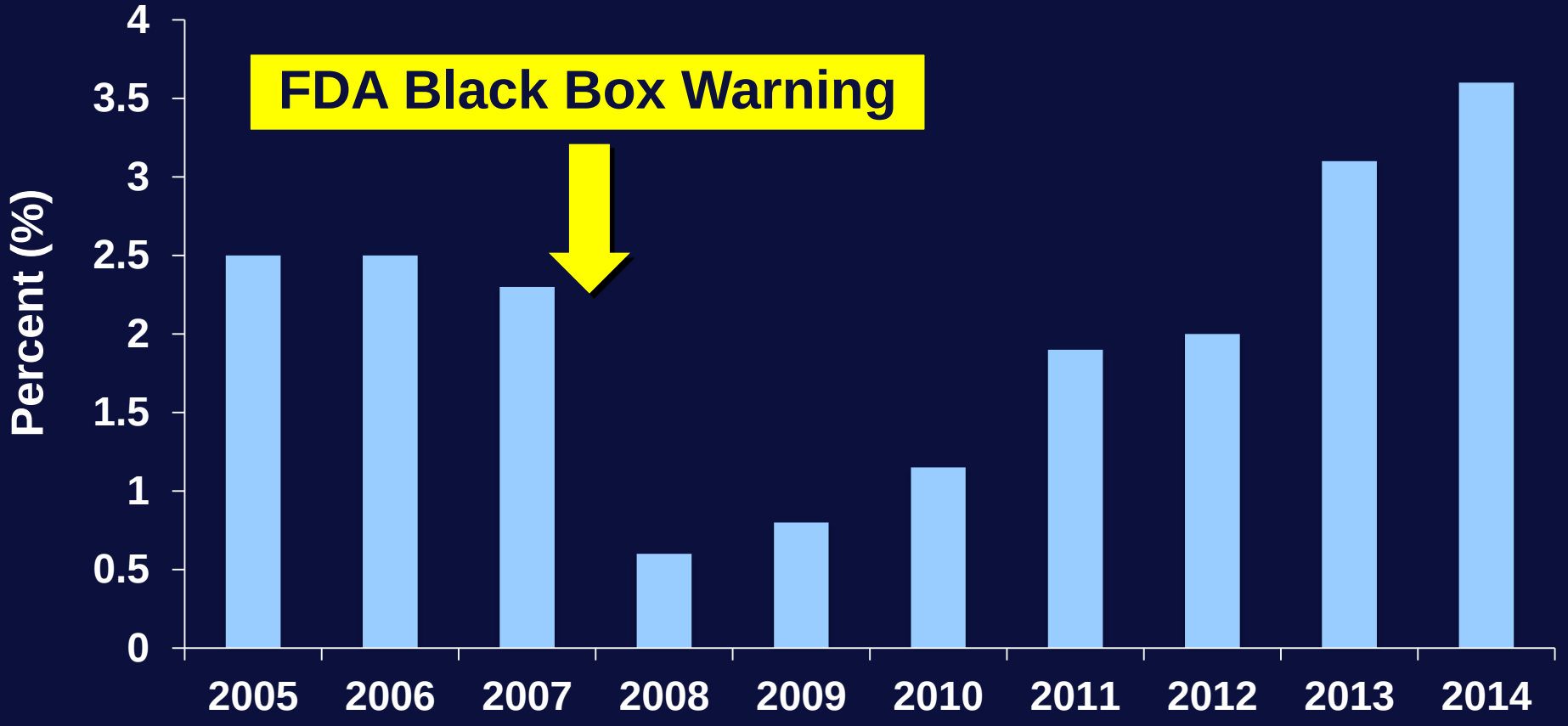
October 12, 2007

- Known or suspected intracardiac shunt
- Hypersensitivity to perflutren (blood products or albumin-Optison)
- Acute MI, worsening or unstable CHF
- Serious ventricular arrhythmias or high risk for arrhythmia
- Respiratory failure
- Severe emphysema, PE or other conditions that cause pulmonary failure
- Hypertension due to compromised pulmonary arterial vasculature

Warning

30 minute period of monitoring

Contrast Echocardiography as % of Total Echo's in the USA



*Through July 2014

Arlington Medical Resources—Courtesy Michael Main

Journal of the American College of Cardiology
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EXPEDITED PUBLICATION

Acute Mortality in Patients Undergoi With and Without

Results in 18,671 Conse

Lisa L. Kusnetzky, BA, Adnar
Philip G. Jones, MS, Michael
Kansas City, Missouri

Objectives We sought to with and witho

Background The U.S. Food perflutren-cont temporally rel To appreciate lation in quest in hospitalized contrast agent

Methods A retrospectiv January 2005 Studies were those perform available for Health Systen Definity and u

Results Of the 18,671 phy, 46 died w (0.42%). There the echocardio 202), patients significant con

Conclusions Approximately risk associate bid conditions American Coll

Ultrasound contrast agents are indicat cardial border delineation in patients w cult echocardiographic examinations (utility in the diagnosis and manage

From the Saint Luke's Mid America Heart Institute, Main has received research support from and has a POINT Biomedical, Acusphere, Inc., and Bristol-Mye

Manuscript received January 16, 2008; revised man 2008, accepted March 5, 2008.

JACC: CARDIOVASCULAR IMAGING
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Safety of Contrast Agent U Stress Echocardiography

A 4-Year Experience From a Single-Center

Sahar S. Abdelmoneim, MD, MSc,*‡ Mathieu Ber
Abhijeet Dhoble, MD, MPH,* Sue Ann C. Ness,
Stuart Moir, MD,* Robert B. McCully, MD,* Patr
Sharon L. Mulvagh, MD*
Rochester, Minnesota; and Assiut, Egypt

OBJECTIVES We evaluated the short- and long echocardiography (SE).

BACKGROUND Concerns about contrast agent sa use in the U.S.

METHODS We studied 26,774 patients who unc December 31, 2007. The 10,792 patients who comprised perfluorocarbon-based agents for left ventricular opa comprised 15,982 patients who had their first SE in Short-term (≤72 h and ≤30 days) and long-term (up to infarction (MI). Cox regression models were used. Immed also reported.

RESULTS The contrast cohort had older patients (years; $p < 0.001$), a higher percentage of males (57.4% compared with the noncontrast cohort. In addition, dob exercise SE patients. Abnormal SE findings in patients w (32.4% vs. 27.9%, $p < 0.001$). The 2 cohorts had no sta events (death and MI). Within 72 h, 1 patient in the co cohort died ($p = 0.54$); 3 in the contrast cohort and 7 in t 30 days, 37 patients (0.34%) in the contrast cohort and died ($p = 0.85$); 17 patients (0.16%) in the contrast co cohort had MI ($p = 0.19$). Adjusted hazard ratios were nc confidence interval: 0.88 to 1.11) or MI (0.99; 95% conf

CONCLUSIONS The use of contrast agents du short-term or long-term risk of death or MI. (J Am C American College of Cardiology Foundation

From the *Division of Cardiovascular Diseases and the †Division of Biosta ‡Division of Cardiovascular Diseases, Assiut University, Assiut, Egypt. Lantheus Medical Imaging, GE Healthcare, and Astellas Pharma Inc.

Manuscript received January 9, 2009; revised manuscript received March

CLINICAL INVESTIGATIONS
CONTRAST ECHOCARDIOGRAPHY

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

Kevin Wei, MD, Sharon L. Mulvagh, MD, Lisa Carson, MSc, Ravin Davidoff, MD, Ruvin Gabriel, MB, ChB, Richard A. Grimm, DO, Stephanie Wilson, MD, Lorrie Fane, RDCS, Charles A. Herzog, MD, William A. Zoghbi, MD, FASE, Rhonda Taylor, AS, RDCS, Michael Farrar, MD, Farooq A. Chaudhry, MD, Thomas R. Porter, MD, Waleed Irani, MD, FASE, and Roberto M. Lang, MD, FASE,
Portland, Oregon; Rochester, Minnesota; Memphis, Tennessee; Boston, Massachusetts; Cleveland, Ohio; Alberta, Canada; Minneapolis, Minnesota; Houston, Texas; Kansas City, Missouri; New York City, New York; Omaha, Nebraska; Nashville, Tennessee; and Chicago, Illinois

Background: The purpose of this retrospective analysis was to define the incidence of severe adverse events after exposure to ultrasound contrast agents.

Methods: Data between January 1, 2001, and September 30, 2007, were collected using invited responses to an on-line web-based questionnaire from 1 general and 12 cardiac ultrasound laboratories. During a period of 4.5 ± 2.4 years, a total of 66,164 doses of Definity (Lantheus Medical Imaging, North Billerica, MA) and 12,219 doses of Optison (GE Healthcare, Buckinghamshire, UK) were administered, reflecting contrast use in 5% of transthoracic and 28% of stress echocardiographic procedures. More than 10,000 doses were given to critically ill patients in intensive care unit settings or to patients with acute chest pain of suspected cardiac origin. The median age of patients who received an ultrasound contrast agent was 60 years, 49% were male, and the mean body mass index was 32 ± 1.4 g/m^{-2}.

Results: Severe reactions that were considered "probably" related to an ultrasound contrast agent developed in 8 patients (0.01%), all of whom were outpatients, and 4 (0.006%) of these were consistent with anaphylactoid reactions. There were no deaths reported. All patients recovered with treatment. No serious events were seen in inpatients.

Conclusion: This multicenter, retrospective analysis includes the largest number of doses of ultrasound contrast agents ever published and a large number of patients evaluated in a wide variety of settings, including the critically ill. It shows that these agents have a good safety profile in both cardiac and abdominal ultrasound applications. The incidence of severe adverse reactions to ultrasound contrast agents is no greater, and may be lower, than that reported for contrast agents commonly used in other cardiac imaging tests. (J Am Soc Echocardiogr 2008;21:1202-1206.)

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

Because of post-marketing surveillance reports of 4 patient deaths that were temporally related to the administration of perflutren-containing ultrasound contrast agents, the US Food and Drug Administration (FDA) issued a "black box" warning for Definity (Lantheus Medical Imaging, North Billerica, MA) and Optison (GE Healthcare, Buckinghamshire, UK) on October 12, 2007.[1,2]

From the Oregon Health and Science University, Portland, Oregon (K.W.); Mayo Clinic, Rochester, Minnesota (S.L.M.); Baptist Memphis Department of Echocardiography, Memphis, Tennessee (L.C.); Boston Medical Center, Boston, Massachusetts (R.D.); Cleveland Clinic, Cleveland, Ohio (R.G., R.A.G.); Foothills Medical Centre, Calgary, Alberta, Canada (S.W.); Hennepin Heart Center at Hennepin County Medical Center, University of Minnesota, Minneapolis, Minnesota (L.F., C.H.); Methodist DeBakey Heart and Vascular Center, Houston, Texas (W.A.Z.); North Kansas City Hospital, North Kansas City, Missouri (R.T., M.F.); St. Luke's-Roosevelt Hospital Center, Columbia University College of Physicians & Surgeons, New York, NY (F.A.C.); University of Nebraska Medical Center, Omaha, Nebraska (T.R.P.); Vanderbilt Heart and Vascular Institute, Nashville, Tennessee (W.I.); and the University of Chicago, Chicago, Illinois (R.M.L.).

Disclosures: Research grants from GE Healthcare (K.W., S.L.M.), Lantheus Medical Imaging (S.L.M., S.W., F.A.C., T.R.P.); POINT Biomedical (F.A.C.); ImaRx Therapeutics (T.R.P.); Siemens Medical (T.R.P.). Speaker's bureau/honoraries/expert witness: Lantheus Medical Imaging (F.A.C., T.R.P., W.I., R.L.); ImaRx Therapeutics Inc. (T.R.P.); Acusphere (R.L.); POINT Biomedical (R.L.). Stock Ownership: GE Healthcare (C.H.). Consultant/advisory board/steering committees: Acusphere (K.W., S.L.M., T.R.P.); POINT Biomedical (K.W., S.L.M., T.R.P.); Siemens Medical (S.W.); Philips Ultrasound (S.W.).

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EXPEDITED PUBLICATION **Short Original Research Paper**

Acute Mortality in Hospitalized Patients Undergoing Echocardiography With and Without an Ultrasound Contrast Agent

Results in 18,671 Consecutive Studies

Lisa L. Kusnetzky, BA, Adnan Khalid, MD, Taiyeb M. Khumri, MD, Tabitha G. Moe, MD, Philip G. Jones, MS, Michael L. Main, MD, FACC

Kansas City, Missouri

Conclusions: Approximately 0.4% of hospitalized patients die within 24 h of echocardiography. There is no increased mortality risk associated with Definity-enhanced examinations, despite evidence for higher clinical acuity and more comorbid conditions in patients undergoing contrast studies.

Conclusions Approximately 0.4% of hospitalized patients die within 24 h of echocardiography. There is no increased mortality risk associated with Definity-enhanced examinations, despite evidence for higher clinical acuity and more comorbid conditions in patients undergoing contrast studies. (J Am Coll Cardiol 2008;51:1704–6) © 2008 by the American College of Cardiology Foundation

Ultrasound contrast agents are indicated to enhance endocardial border delineation in patients with technically difficult echocardiographic examinations (1) and have proven utility in the diagnosis and management of critically ill patients (2–4). On October 10, 2007, the U.S. Food and Drug Administration issued new boxed warnings and contraindications for the ultrasound contrast agents Optison (GE Healthcare, Buckinghamshire, United Kingdom) and Definity (Bristol-Myers Squibb Medical Imaging, Billerica, Massachusetts), effectively restricting their use in patients with acute coronary syndromes (ACS), worsening or decompensated heart failure (HF), and respiratory failure (5). These warnings were largely based on reports of 4 deaths occurring during or immediately after Definity injection (5).

From the Saint Luke's Mid America Heart Institute, Kansas City, Missouri. Dr. Main has received research support from and has a consultant relationship with POINT Biomedical, Acusphere, Inc., and Bristol-Myers Squibb Medical Imaging.

Manuscript received January 16, 2008; revised manuscript received February 26, 2008, accepted March 5, 2008.

Safety of Contrast Agent Use During Stress Echocardiography

A 4-Year Experience From a Single-Center Cohort Study of 26,774 Patients

Sahar S. Abdelmoneim, MD, MSc, Mathieu Bernier, MD, Christopher G. Scott, MS, Abhijeet Dhoble, MD, MPH, Sue Ann C. Ness, RN, Mary E. Hagen, RDCS, Stuart Moir, MD, Robert B. McCully, MD, Patricia A. Pellikka, MD, Sharon L. Mulvagh, MD

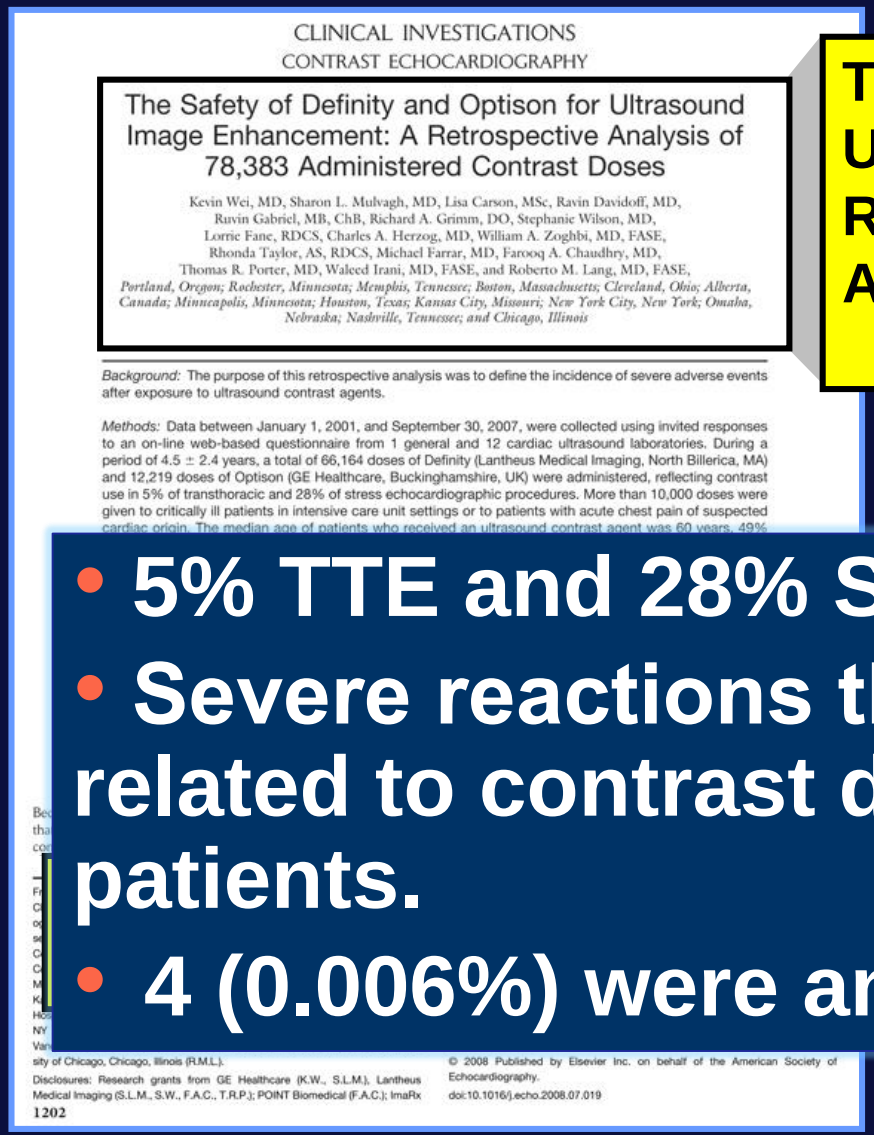
December 31, 2007. The 10,792 patients who comprised the contrast cohort received second-generation perfluorocarbon-based agents for left ventricular opacification during SE. The noncontrast cohort comprised 15,982 patients who had their first SE in the same period but without contrast agents. Short-term (≤72 h and ≤30 days) and long-term (up to 4.5 years) end points were death and myocardial

Conclusions: The use of contrast agents during SE was not associated with an increased short-term or long-term risk of death or MI.

died (p = 0.85); 17 patients (0.16%) in the contrast cohort and 16 patients (0.10%) in the noncontrast cohort had MI (p = 0.19). Adjusted hazard ratios were not different between cohorts for death (0.99; 95% confidence interval: 0.88 to 1.11) or MI (0.99; 95% confidence interval: 0.80 to 1.22).

CONCLUSIONS The use of contrast agents during SE was not associated with an increased short-term or long-term risk of death or MI. (J Am Coll Cardiol Img 2009;2:1048–56)

J. Am Coll Cardiol Img 2009;2:2048-56



CLINICAL INVESTIGATIONS
CONTRAST ECHOCARDIOGRAPHY

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

Kevin Wei, MD, Sharon L. Mulvagh, MD, Lisa Carson, MSc, Ravin Davidoff, MD, Ruvin Gabriel, MB, ChB, Richard A. Grimm, DO, Stephanie Wilson, MD, Lorrie Fane, RDCS, Charles A. Herzog, MD, William A. Zoghbi, MD, FASE, Rhonda Taylor, AS, RDCS, Michael Farrar, MD, Farooq A. Chaudhry, MD, Thomas R. Porter, MD, Waleed Irani, MD, FASE, and Roberto M. Lang, MD, FASE,
Portland, Oregon; Rochester, Minnesota; Memphis, Tennessee; Boston, Massachusetts; Cleveland, Ohio; Alberta, Canada; Minneapolis, Minnesota; Houston, Texas; Kansas City, Missouri; New York City, New York; Omaha, Nebraska; Nashville, Tennessee; and Chicago, Illinois

Background: The purpose of this retrospective analysis was to define the incidence of severe adverse events after exposure to ultrasound contrast agents.

Methods: Data between January 1, 2001, and September 30, 2007, were collected using invited responses to an on-line web-based questionnaire from 1 general and 12 cardiac ultrasound laboratories. During a period of 4.5 ± 2.4 years, a total of 66,164 doses of Definity (Lantheus Medical Imaging, North Billerica, MA) and 12,219 doses of Optison (GE Healthcare, Buckinghamshire, UK) were administered, reflecting contrast use in 5% of transthoracic and 28% of stress echocardiographic procedures. More than 10,000 doses were given to critically ill patients in intensive care unit settings or to patients with acute chest pain of suspected cardiac origin. The median age of patients who received an ultrasound contrast agent was 60 years, 49%

sity of Chicago, Chicago, Illinois (R.M.L.).

Disclosures: Research grants from GE Healthcare (K.W., S.L.M.), Lantheus Medical Imaging (S.L.M., S.W., F.A.C., T.R.P.); POINT Biomedical (F.A.C.); ImaRx

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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 et al.

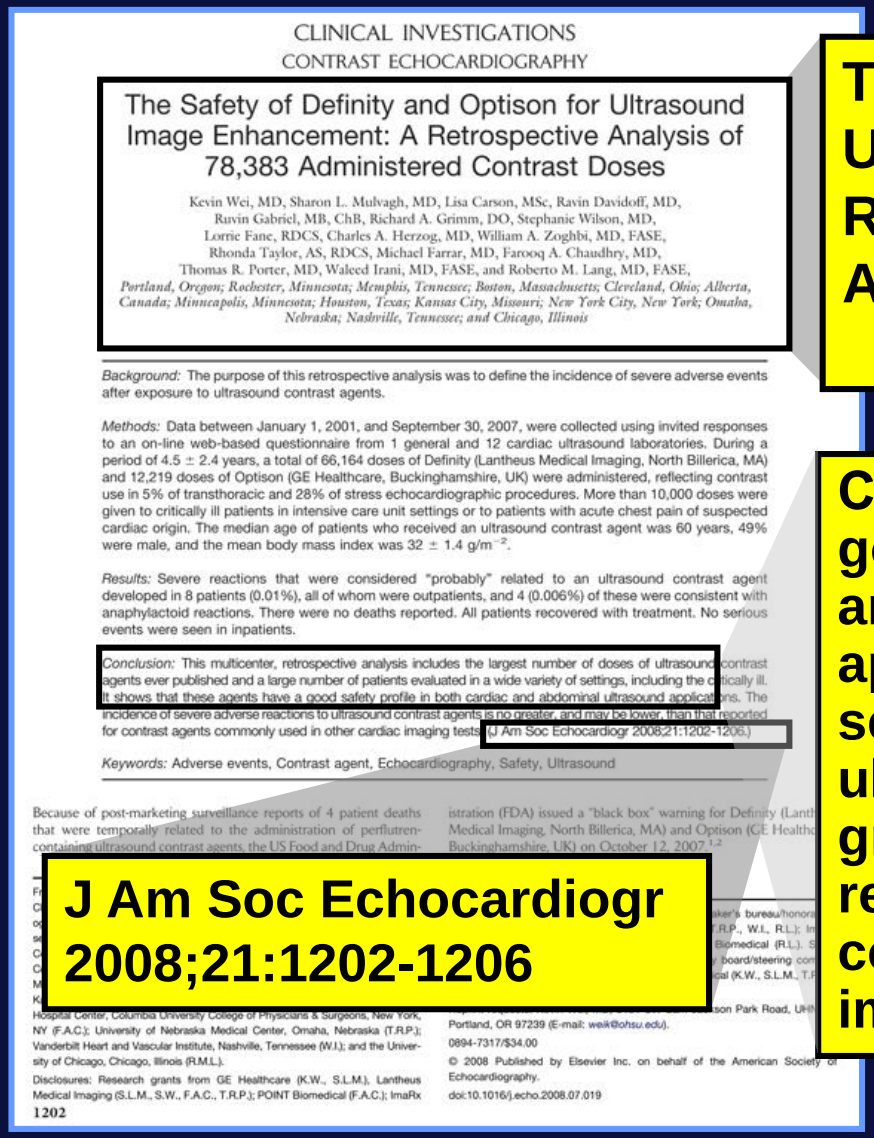
- **5% TTE and 28% SECHO**
- **Severe reactions that were “probably” related to contrast developed in 8 (0.01%) patients.**
- **4 (0.006%) were anaphylactoid reactions**

Ultrasound Contrast Anaphylactoid Reactions

CARPA

Complement Activation Related Pseudo Allergy

- Features similar IgE-mediated Type 1 reactions.
- Angioedema, bronchospasm, hypoxemia, hypotension, low back pain, and urticaria
- Can occur without prior exposure, decrease in severity with subsequent exposure, resolve spontaneously.



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Results: Severe reactions that were considered "probably" related to an ultrasound contrast agent developed in 8 patients (0.01%), all of whom were outpatients, and 4 (0.006%) of these were consistent with anaphylactoid reactions. There were no deaths reported. All patients recovered with treatment. No serious events were seen in inpatients.

Conclusion: This multicenter, retrospective analysis includes the largest number of doses of ultrasound contrast agents ever published and a large number of patients evaluated in a wide variety of settings, including the critically ill. It shows that these agents have a good safety profile in both cardiac and abdominal ultrasound applications. The incidence of severe adverse reactions to ultrasound contrast agents is no greater, and may be lower, than that reported for contrast agents commonly used in other cardiac imaging tests. (J Am Soc Echocardiogr 2008;21:1202-1206.)

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

Because of post-marketing surveillance reports of 4 patient deaths that were temporally related to the administration of perflutren-containing ultrasound contrast agents, the US Food and Drug Administration (FDA) issued a "black box" warning for Definity (Lantheus Medical Imaging, North Billerica, MA) and Optison (GE Healthcare, Buckinghamshire, UK) on October 12, 2007.[1,2]

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J Am Soc Echocardiogr 2008;21:1202-1206

Helen Keller

"Avoiding Danger in the long run is no safer than outright exposure"

Comparable Risk

TEE

- Dental Injury 0.03%
- Esophageal perforation 0.01%

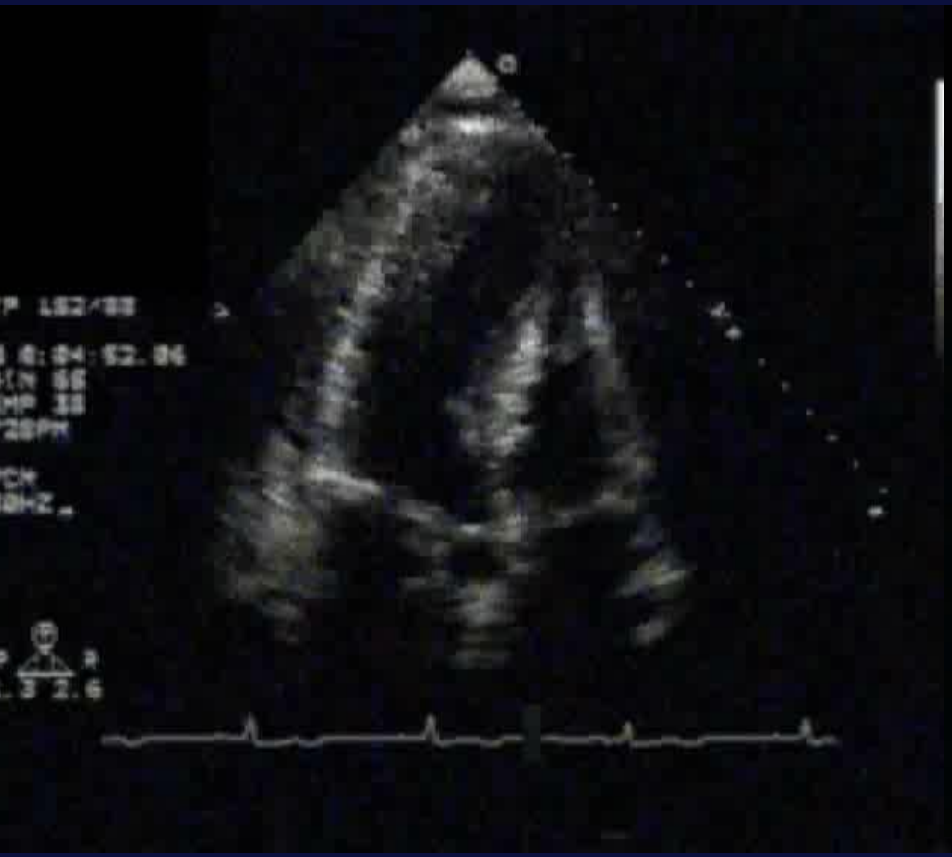
Gadolinium

- Urticarial rash 0.04%
- Anaphylactoid shock 0.01
- Skin fibrosis

Non-ionic contrast

- Urticaria 0.5%
- Severe reactions 0.001-0.04%
- Intra-arterial (cath)
  - Urticaria (0.5%)
  - Hypotension 0.3%
  - Cardiac arrest 0.2%
- Radiation and procedural risk

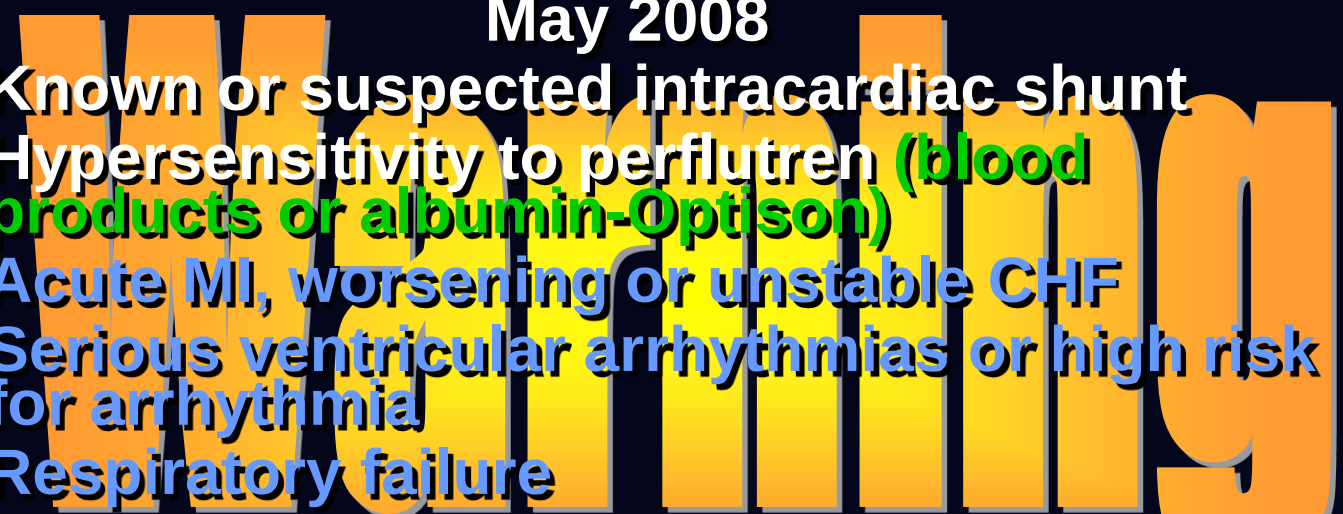
What Is The Risk?



Sir Winston Leonard Spencer Churchill (1874-1965)

"When I look back on all the worries I remember the story of the old man who said on his deathbed that he had a lot of trouble in his life, most of which never happened"

May 2008



May 2008

- Known or suspected intracardiac shunt
- Hypersensitivity to perflutren (blood products or albumin-Optison)
- Acute MI, worsening or unstable CHF
- Serious ventricular arrhythmias or high risk for arrhythmia
- Respiratory failure
- Severe emphysema, PE or other conditions that cause pulmonary
- Hypertension due to compromised pulmonary arterial vasculature

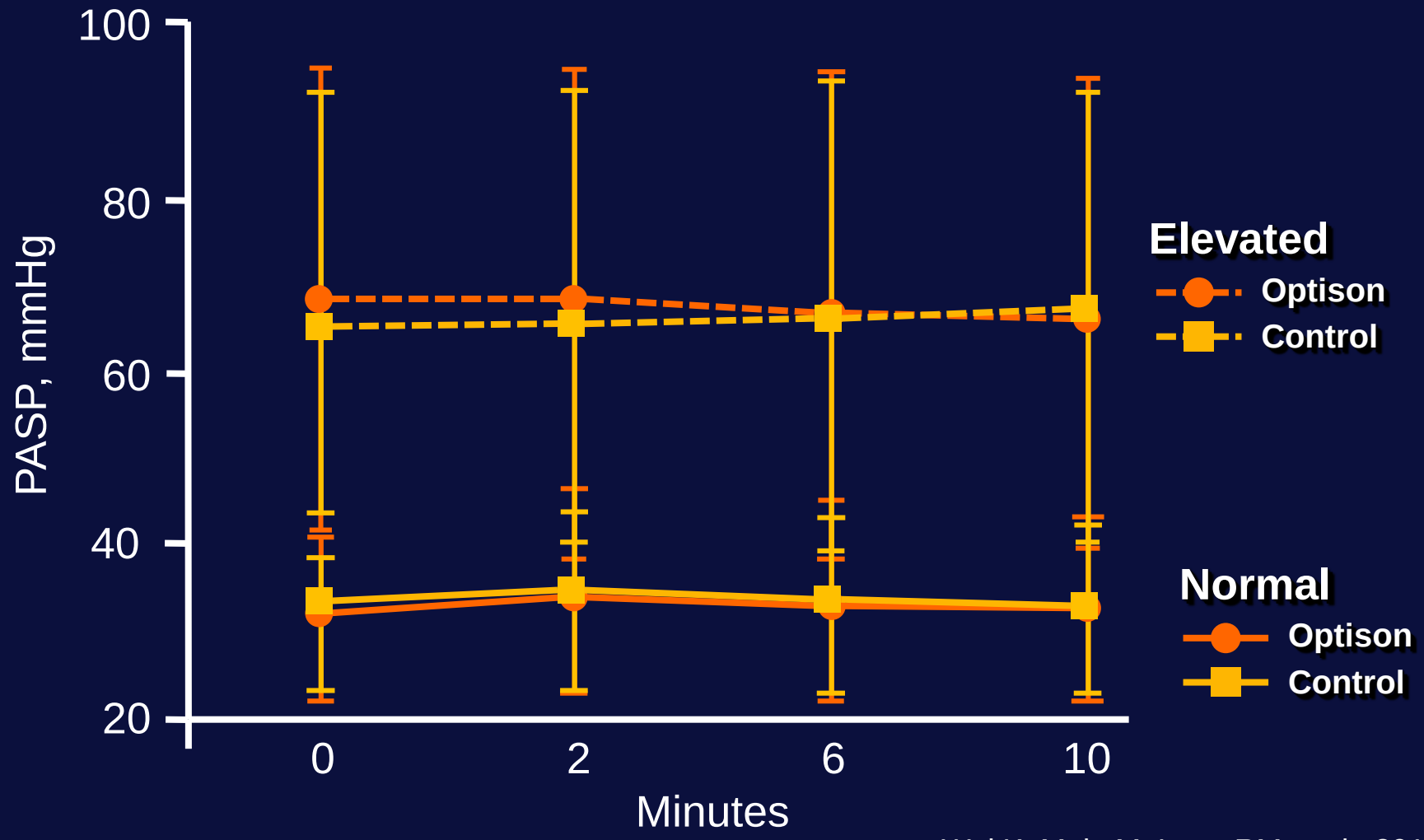
Monitoring

Vitals, ECG, O_2 saturation

30 minutes post injection

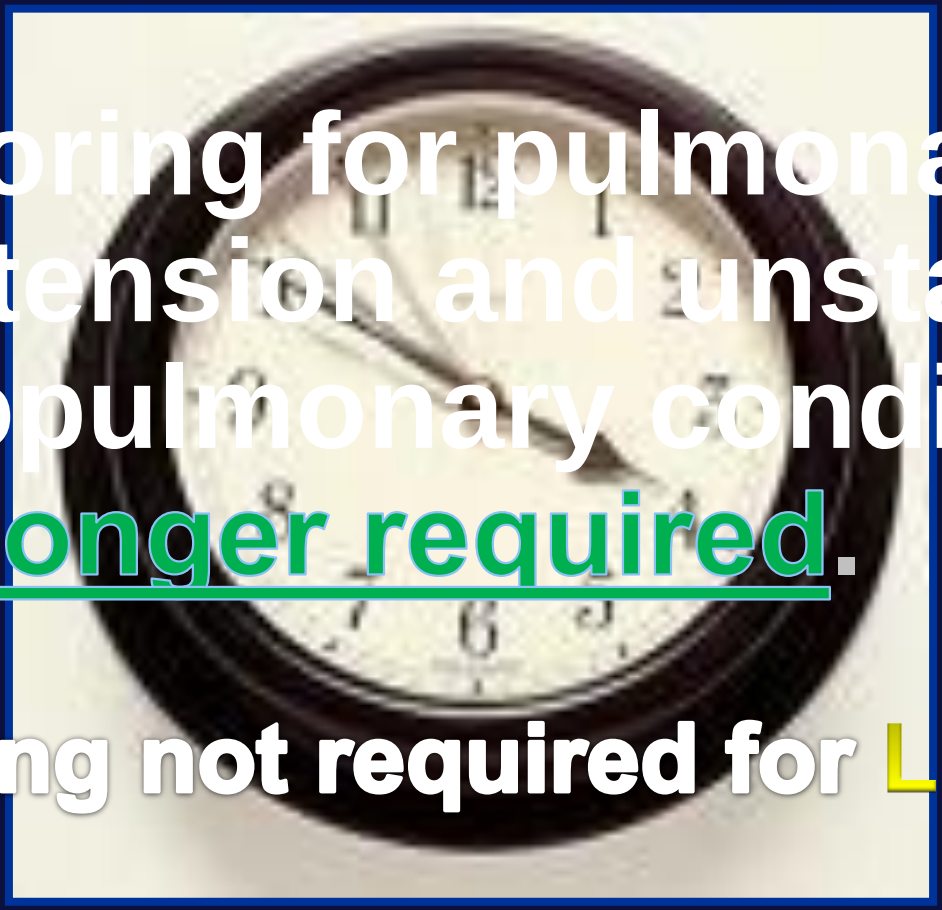
- Pulmonary hypertension
  (TR vel >4.0m/sec)
- Unstable cardiopulmonary conditions

Effect of Contrast On Pulmonary Hemodynamics



Wei K, Main M, Lang RM et al., 2011

October 2011 (Definity)
August 2012 (Optison)



Monitoring for pulmonary hypertension and unstable cardiopulmonary conditions is no longer required.

Monitoring not required for Lumason

GUIDELINES AND STANDARDS

Guidelines for the Cardiac Sonographer in the Performance of Contrast Echocardiography:

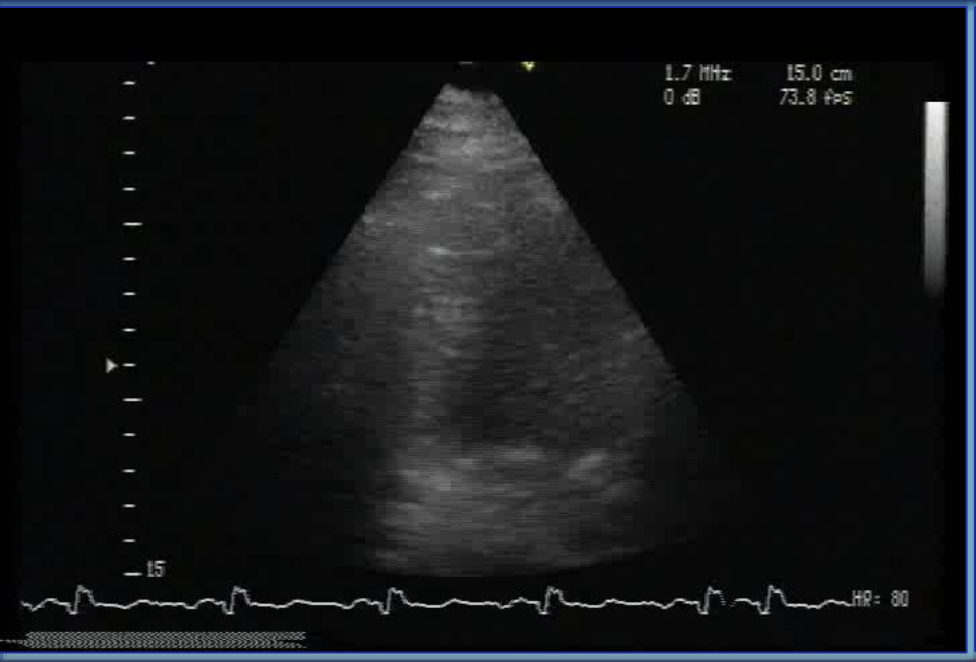
Safety in Patients with Patent Foramen Ovale and Congenital Heart Disease

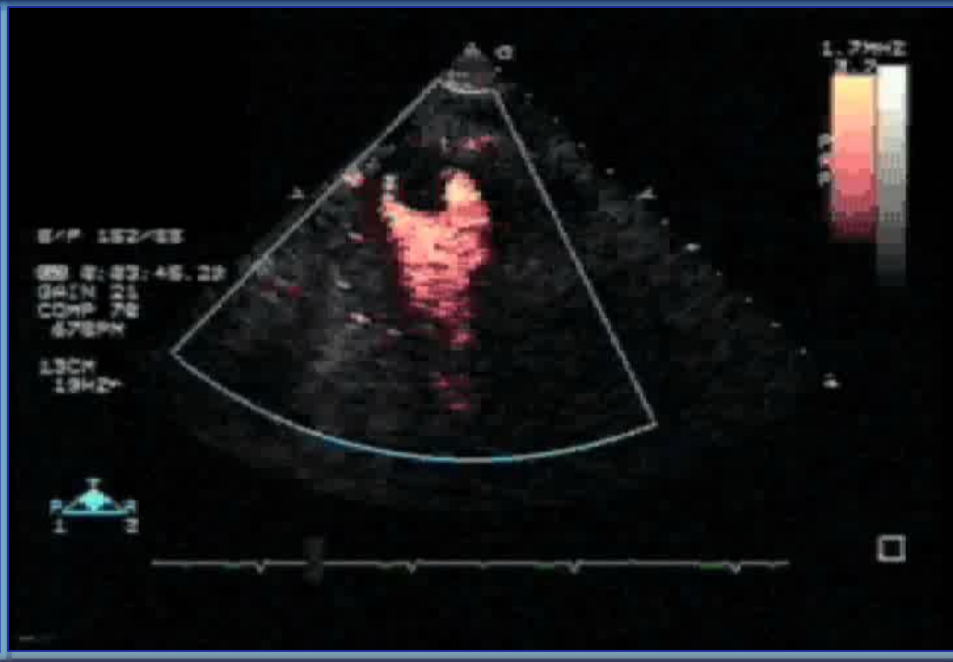
Thomas R. Porter, MD, FASE (Chair), Sahar Abdelmoneim, MD, J. Todd Belcik, BS, RCS, RDCS, FASE

- "Recent large reviews of the literature have failed to detect any increased risk for systemic embolization associated with UCAs in patient populations that obviously included those with PFOs".
- "Therefore, the writing group does not consider patients with small degrees of right-to-left shunting through PFOs (those that result in a transient appearance of saline contrast in the left atrium or ventricle and do not fill the left atrial or LV cavity) at increased risk for UCA use".

Contrast Echocardiography:

Maximizes Value with Minimal Hassle





Take Home Points

1. **The clinical utility of a bubble depends on its size, shell and type of gas**
2. ***The backscattered signal radiating from a bubble that oscillates in a nonlinear fashion* will contain a harmonic component.**

Take Home Points

3. Perfusion:

- Low MI, nondestructive, real time imaging
- High MI, destruction, triggered imaging

4. The only contraindications are known intracardiac shunt and a hypersensitivity to the gas, perflutren (blood products or albumin—Optison only)

Non-Linear Oscillation of Ultrasound Contrast Microbubbles

a. Produce only a harmonic backscatter signal.
b. Produce only a backscatter signal the same as the insonating frequency.
c. Occurs when the microbubble expands and compresses to the same degree as in oscillates in harmony with the pressure waves of the ultrasound field.
d. Occurs only when the microbubbles are sized small enough to pass through the pulmonary capillaries and opacify left sided structures.
e. Is an acoustic behavior of a microbubble that supports real-time perfusion imaging.

Contrast Is Contraindicated in Patients with:

a. Pulmonary hypertension
b. Known intracardiac shunt
c. Unstable CHF
d. Hypersenstivity to the gas (perflutren)
e. b and d
f. All of the above

Microbubble Persistence Is Greatest with?

a. Smaller vs larger bubbles.
b. More compliant less-stiff microbubble shells.
c. High molecular weight based gas filled bubbles.
d. Air filled gas bubbles.
e. b and d


mayo