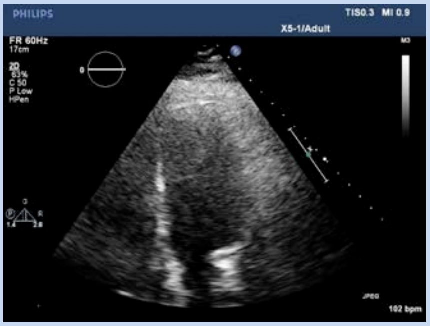

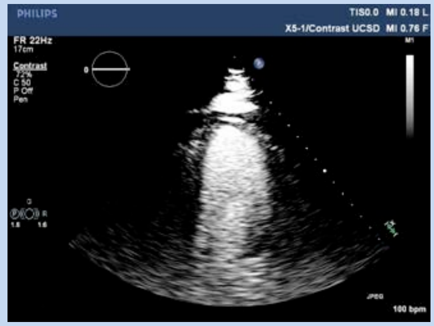

4

A Practical Approach to Echo Contrast

- Studies indicate about 15 to 30% of echo studies are inadequate (1)
  - The definition of inadequate is subjective
  - Stress echoes and those in ICU are more often inadequate
- Data suggests that less than 5% of echo studies receive contrast (2)
- Clearly, contrast echo is majorly underutilized
- Technical and procedural factors contribute greatly to underutilization
- Philosophical outlook on the role of contrast is critical

1. Kurt M et al; JACC: 2009; Waggoner AD et al; JASE:2001; Platts D et al; Crit Care Resuscitation: 2011)
2. Decision Resources LLC, Toronto, Canada

5

Candidates for Contrast Echo

- Patients most likely to benefit from contrast echo include those with
  - Obesity
  - Congestive heart failure
  - Chronic obstructive pulmonary disease
  - Mechanical ventilation
  - Chest deformity (barrel chest)
  - Patients with limited acoustic windows
    - Inadequate imaging of 2/6 segments in any single view
    - Incomplete Doppler velocity profiles

Mulvagh et al. *J Am Soc Echocardiogr*. 2000;13:331.

6

American Society of Echocardiography Consensus Statement on the Clinical Applications of Ultrasonic Contrast Agents in Echocardiography

Sharon L. Mulvagh, MD, FASE, Chair, Harry Rakowski, MD, FASE, Co-Chair, Mani A. Vannan, MBBS, Co-Chair, Sahar S. Abdelmoneim, MD, MSc, Harald Becher, MD, PhD, S. Michelle Bierig, MPH, RDCS, FASE, Peter N. Burns, PhD, Ramon Castello, MD, FASE, Patrick D. Coon, RDCS, FASE, Mary E. Hagen, RDCS, RN, James G. Jollis, MD, Thomas R. Kimball, MD, FASE, Dalane W. Kitzman, MD, Itzhak Kronzon, MD, FASE, Arthur J. Labovitz, MD, FASE, Roberto M. Lang, MD, FASE, Joseph Mathew, MD, FASE, W. Stuart Moir, MBBSc, Sherif F. Nagueh, MD, Alan S. Pearlman, MD, FASE, Julio E. Perez, MD, FASE, Thomas R. Porter, MD, FASE, Judy Rosenbloom, RDCS, FASE, G. Monet Strachan, RDCS, FASE, Srihari Thanigaraj, MD, FASE, Kevin Wei, MD, Anna Woo, MD, Eric H. C. Yu, MD, and William A. Zoghbi, MD, FASE,

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SYNOPSIS OF SUGGESTED APPLICATIONS FOR ULTRASOUND CONTRAST AGENT USE

- In difficult-to-image patients presenting for rest echocardiography with reduced image quality
  - To enable improved endocardial visualization and assessment of left ventricular (LV) structure and function when ≥2 contiguous segments are not seen on noncontrast images
  - To reduce variability and increase accuracy in LV volume and LV ejection fraction (LVEF) measurements by 2-dimensional (2D) echocardiography
  - To increase the confidence of the interpreting physician in LV functional, structure, and volume assessments
- In difficult-to-image patients presenting for stress echocardiography with reduced image quality
  - To obtain diagnostic assessment of segmental wall motion and thickening at rest and stress
  - To increase the proportion of diagnostic studies
  - To increase reader confidence in interpretation
- In all patients presenting for rest echocardiographic assessment of LV systolic function (not solely difficult-to-image patients)
  - To reduce variability in LV volume measurements through 2D echocardiography
    - To increase the confidence of the interpreting physician in LV volume measurement
- To confirm or exclude the echocardiographic diagnosis of the following LV structural abnormalities, when nonenhanced images are suboptimal for definitive diagnosis
  - Apical variant of hypertrophic cardiomyopathy
  - Ventricular noncompaction
  - Apical thrombus
  - Complications of myocardial infarction, such as LV aneurysm, pseudoaneurysm, and myocardial rupture
- To assist in the detection and correct classification of intracardiac masses, including tumors and thrombi
- For echocardiographic imaging in the intensive care unit (ICU) when standard tissue harmonic imaging does not provide adequate cardiac structural definition
  - For accurate assessment of LV volumes and LVEF
  - For exclusion of complications of myocardial infarction, such as LV aneurysm, pseudoaneurysm, and myocardial rupture
- To enhance Doppler signals when a clearly defined spectral profile is not visible and is necessary to the evaluation of diastolic and/or valvular function

8

Guidelines

ESC European Society of Cardiology

European Heart Journal - Cardiovascular Imaging (2017) **18**, 1205
doi:10.1093/ehjci/jex182

EACVI RECOMMENDATIONS

Clinical practice of contrast echocardiography: recommendation by the European Association of Cardiovascular Imaging (EACVI) 2017

Roxy Senior[1]*, Harald Becher[2], Mark Monaghan[3], Luciano Agati[4], Jose Zamorano[5], Jean Louis Vanoverschelde[6], Petros Nihoyannopoulos[7], Thor Edvardsen[8], and Patrizio Lancellotti[9]

Reviewers: This document was reviewed by members of the EACVI Scientific Documents Committee for 2014–16 and 2016–18: Victoria Delgado, Alessia Gimelli, Bernard Cosyns, Bernhard Gerber, Erwan Donal, Frank Flachskampf, Kristina Haugaa, Nuno Cardim, Pier Giorgio Masci.

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EACVI Indications for Contrast Echo

- Endocardial Border Recognition – ***Should***
  - Two or more contiguous LV segments not visualized
  - When management dependent upon accurate measurement of LVEF
  - When identification of regional wall motion abnormalities is critical
- Cardiac Structure – ***May Be***
  - apical hypertrophy and diverticula, pseudoaneurysm, myocardial rupture, non-compaction and LV thrombi ***are suspected***
- Left Atrial Appendage and Aortic Syndromes- ***May Be***
- Stress Echo – ***Should***
  - Two continuous segments not visualized
  - Presence of deep inspiration
  - For myocardial perfusion
- Myocardial Perfusion – ***May Be*** (If expertise exists)
  - To improve accuracy of stress echo
  - To assess viability

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Who *Must* Have Contrast LVO?

- *Indication* for echo is evaluate LV function
- Endocardial border not visualized in either apical or *non-apical views*
- *LV shape* difficult to determine
- *Epicardial motion* not or poorly visualized
- Reproducibility is of paramount importance

- High suspicion of a structural lesion
  - Mass, apical HCM, Noncompaction

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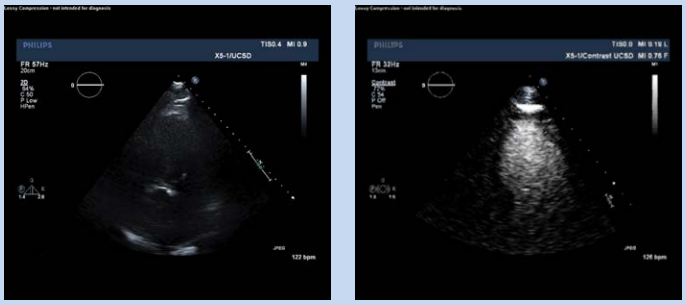
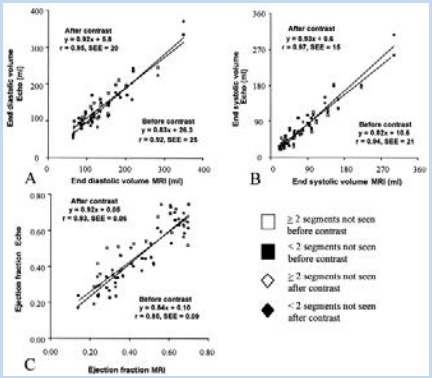
Endocardial Border Definition
68 yo male with AS



12

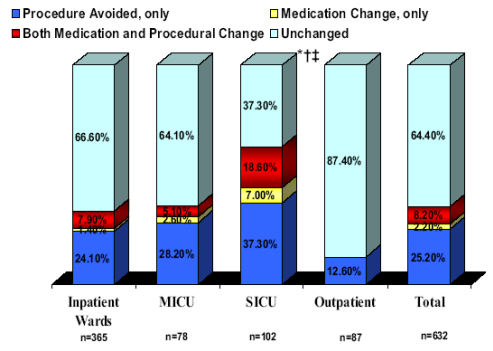
Contrast LVO for LV Volumes/EF vs MRI



Hundley et al; JACC, 1998

14

Impact of LVO on Management



Kurt et al: JACC, 2009

15

Contrast Echo Other Than Border Definition

- Cardiac Shunts
- Doppler enhancement
- Cardiac Masses
  - Tumor vs Clot
- 3D enhancement
- Noncompaction
- Vascular enhancement

16

CONTRAST ECHO

- ***Effective contrast agents***
- ***Refined recording techniques***
- LV cavity opacification
- Doppler enhancement
- Myocardial perfusion
- Delivery of markers, drugs, therapy

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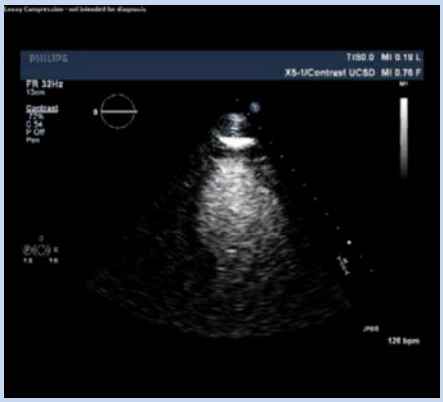
68 yo male with AS



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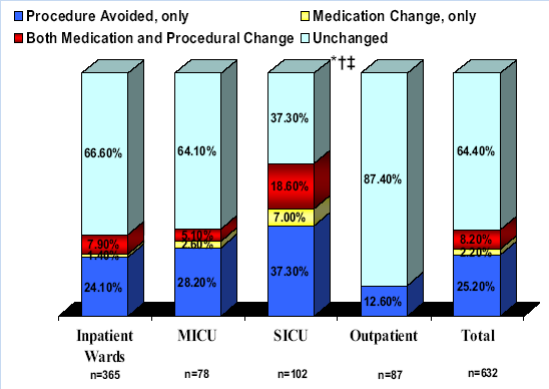
Impact of LVO on Management



Kurt et al: JACC, 2009

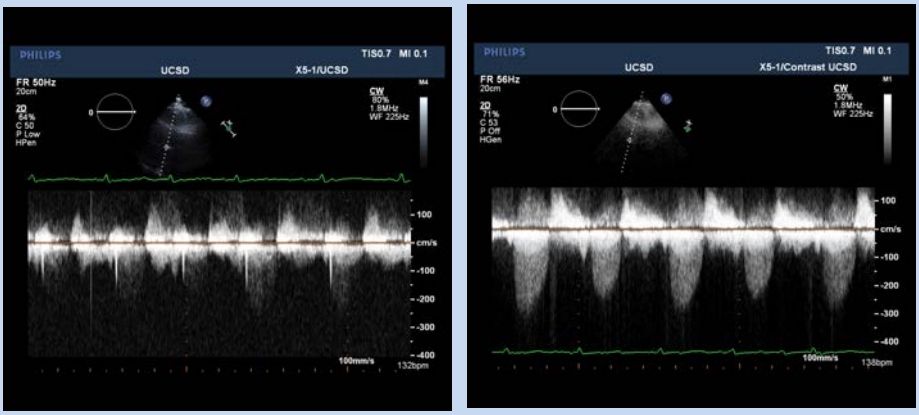
38

Contrast Echo Other Than Border Definition

- Cardiac Shunts
- Doppler enhancement
- Cardiac Masses
  - Tumor vs Clot
- 3D enhancement
- Noncompaction
- Vascular enhancement

41

68 yo male with AS



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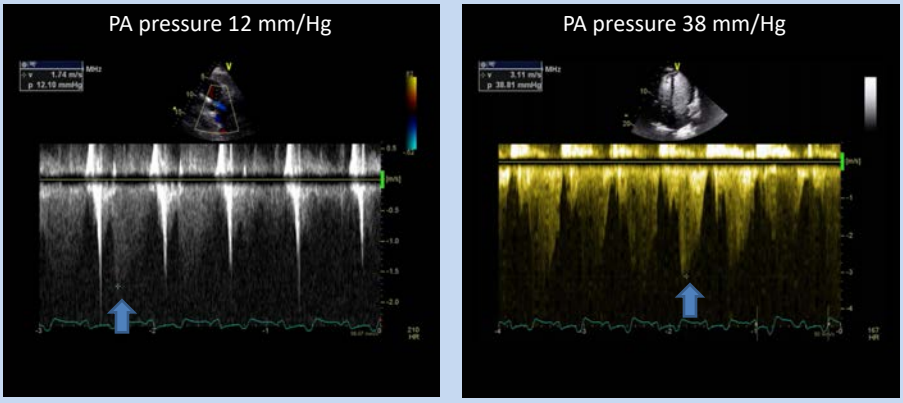
Contrast Enhancement of TR



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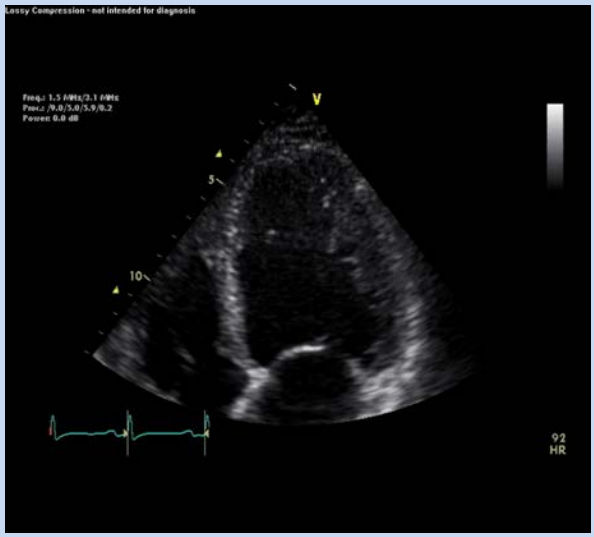
62 yo female Post MI



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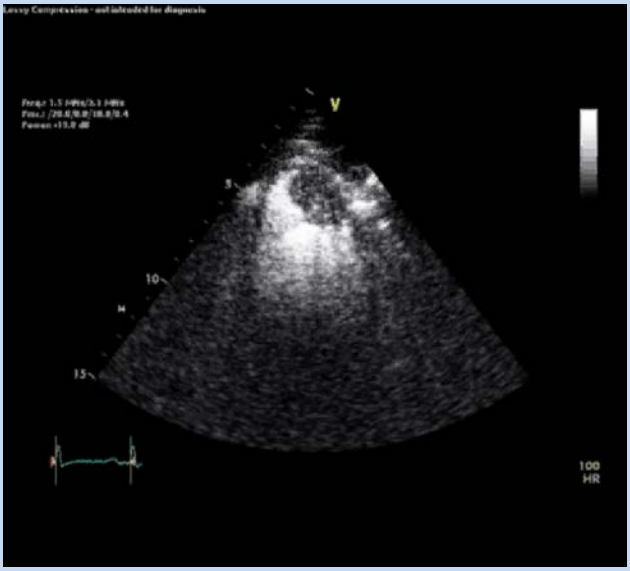

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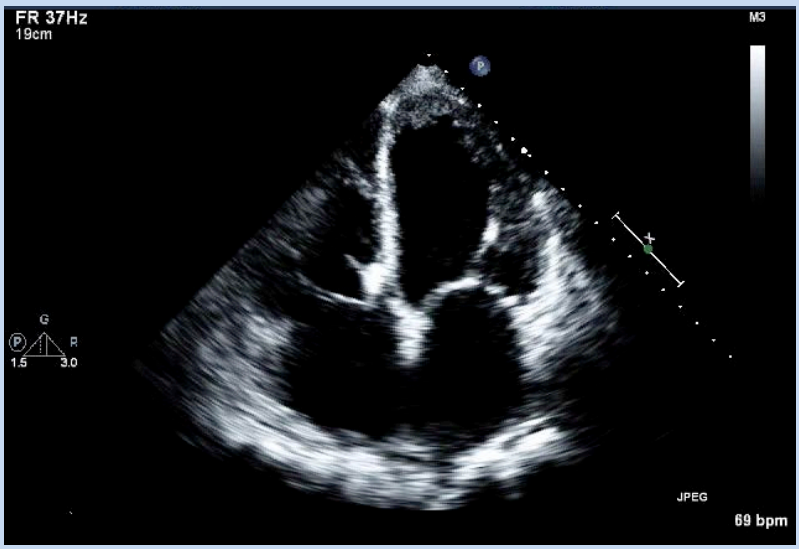
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G
P
R
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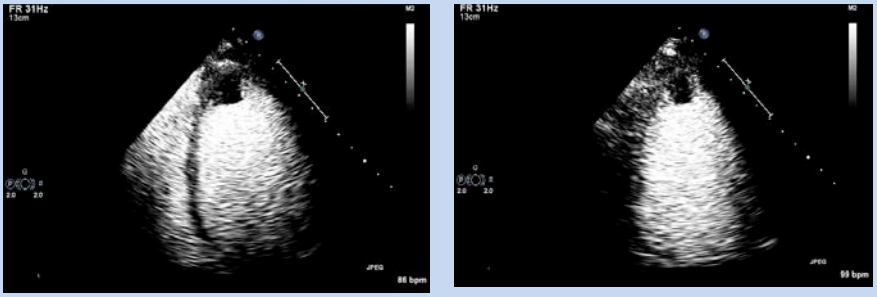
3.0
JPEG
69 bpm

64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86 bpm
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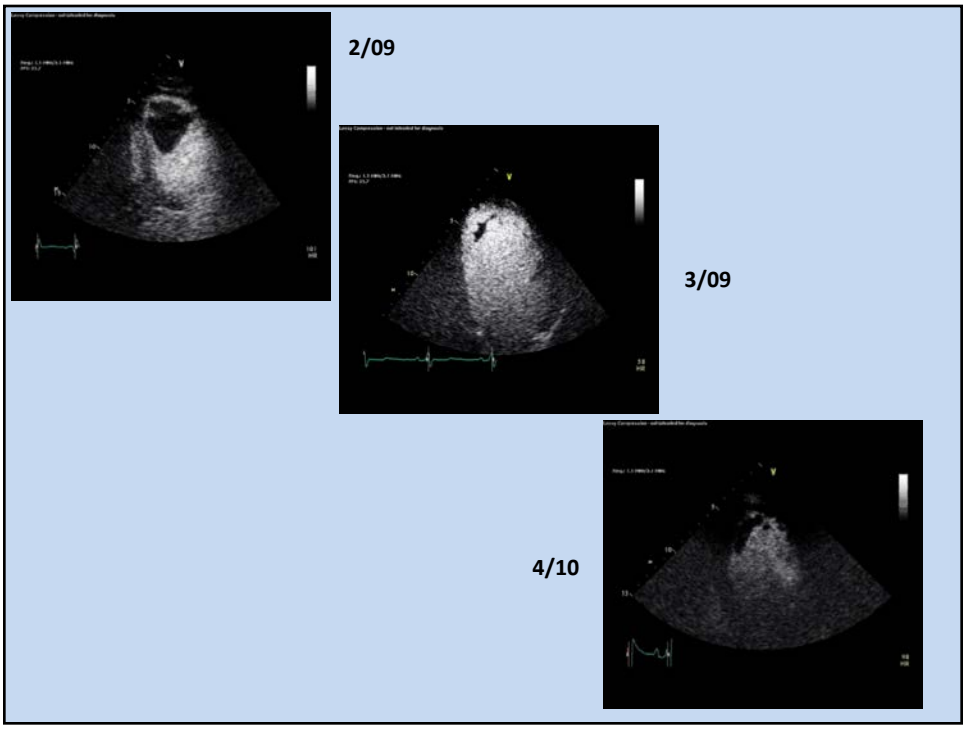
13cm
M2
JPEG
98 bpm

65



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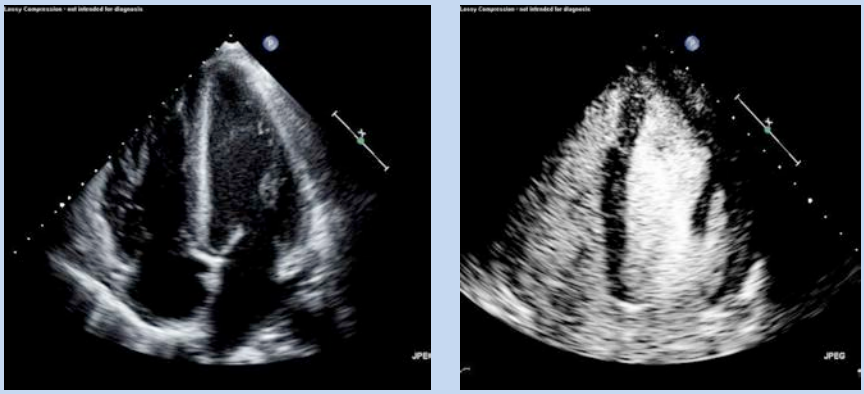
Artifact vs Stasis by Contrast



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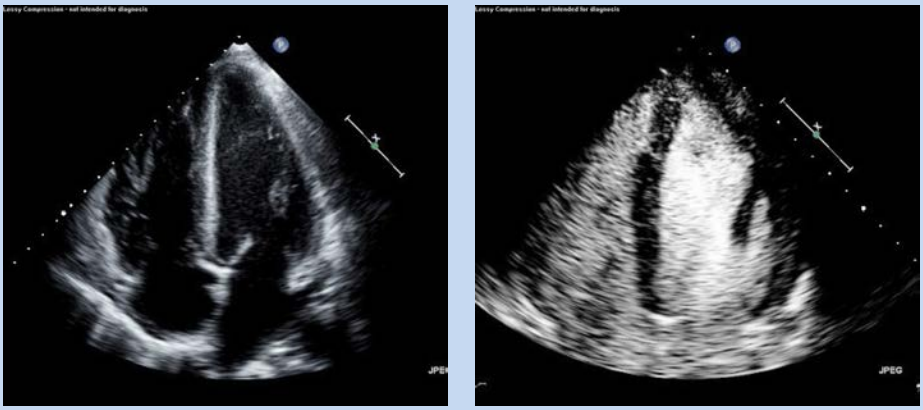
Artifact vs Stasis by Contrast



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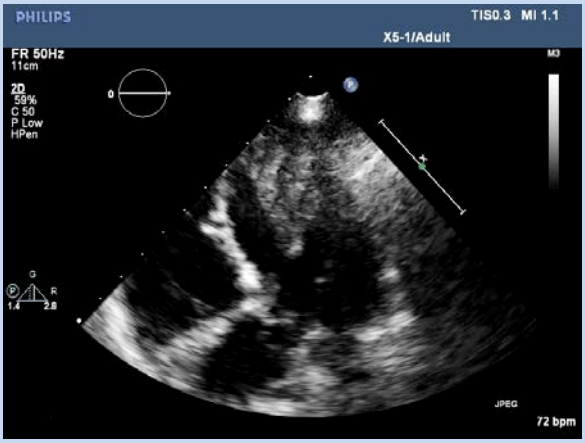
Tumor Perfusion



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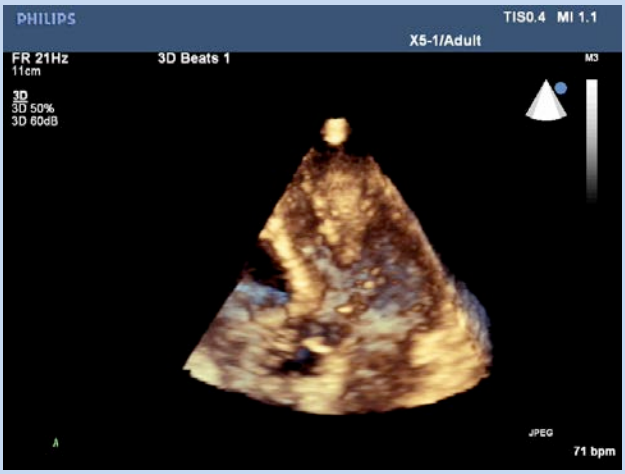
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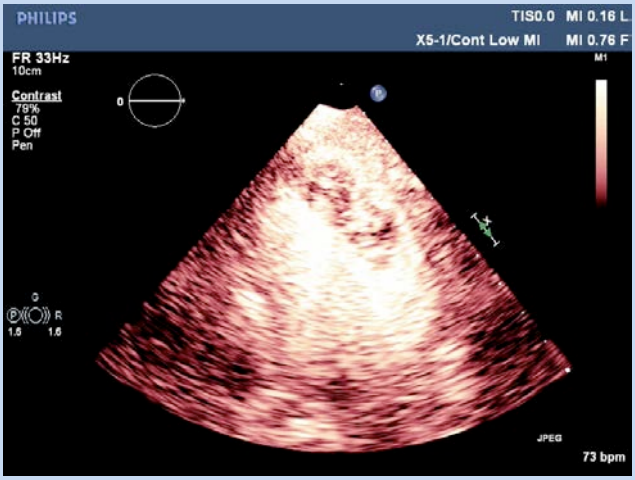
78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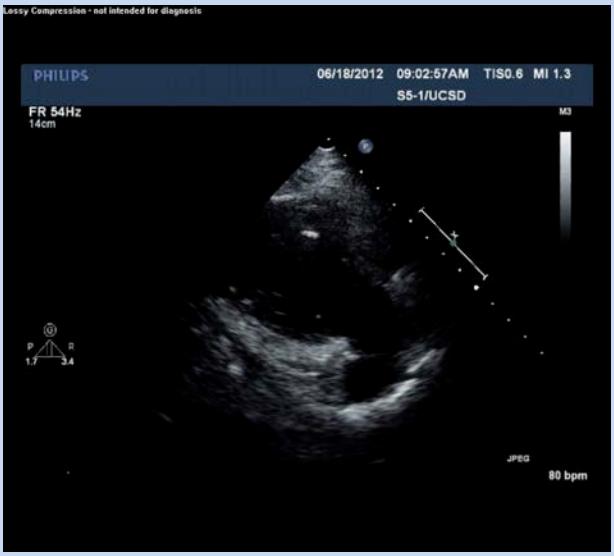
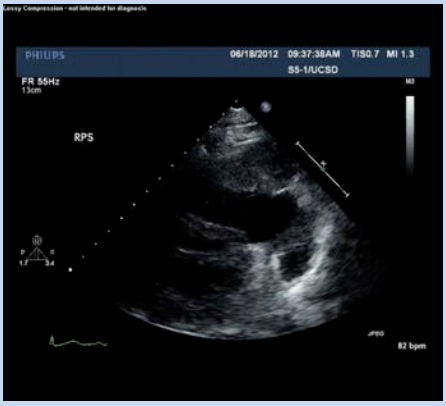
79



80

Tumor vs Clot by Contrast



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doi:10.1016/j.jacc.2003.09.065

Cardiac Imaging

Differential Diagnosis of Cardiac Masses Using Contrast Echocardiographic Perfusion Imaging

James N. Kirkpatrick, MD, Tiffany Wong, MD, James E. Bednarz, BS, RDCS, Kirk T. Spencer, MD, FACC, Lissa Sugeng, MD, R. Parker Ward, MD, FACC, Jeanne M. DeCara, MD, FACC, Lynn Weinert, BS, Thomas Krausz, MD, FRCPATH, Roberto M. Lang, MD, FACC

Chicago, Illinois

OBJECTIVES We investigated the usefulness of echocardiographic contrast perfusion imaging in differentiating cardiac masses.

BACKGROUND Two-dimensional echocardiography is the primary diagnostic modality for cardiac masses. However, differentiation between the different types of cardiac masses may be difficult at times. We hypothesized that echocardiographic contrast perfusion imaging would differentiate the neo-vascularization of malignancies from the avascularity of thrombi and the sparse vascularity of stromal tumors.

METHODS Sixteen patients with cardiac masses underwent power-modulation imaging after echocardiographic intravenous contrast administration. Pixel intensities in the mass and an adjacent

In seven of 16 patients, contrast enhancement resulted in greater pixel intensity in the mass than in the adjacent myocardium. All of these masses were classified pathologically as malignant (n 6) or benign and vascular (n 1). Nine masses demonstrated decreased pixel intensity, compared with the myocardium, and were diagnosed pathologically as myxomas (n 2) or thrombi (n 5), or they resolved with anticoagulation (n 2).

vessel area index ($r = 0.60$).

CONCLUSIONS Echocardiographic contrast perfusion imaging aids in the differentiation of cardiac masses. Compared with the adjacent myocardium, malignant and vascular tumors hyper-enhanced, whereas stromal tumors and thrombi hypo-enhanced. (J Am Coll Cardiol 2004;43:1412–9)

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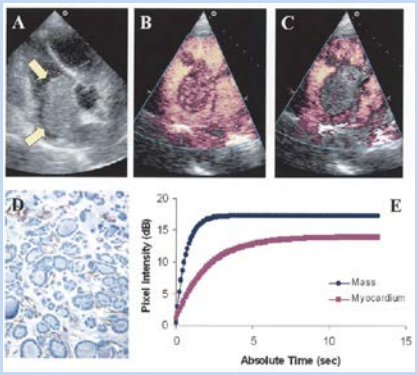
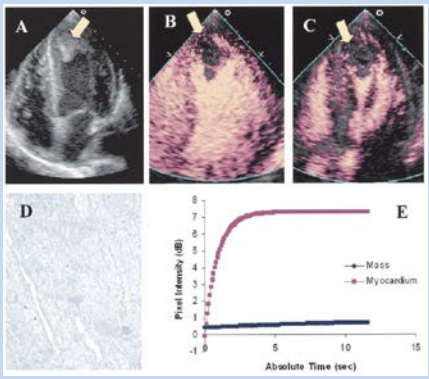
Tumor vs Thrombus by Contrast

Tumor



Thrombus



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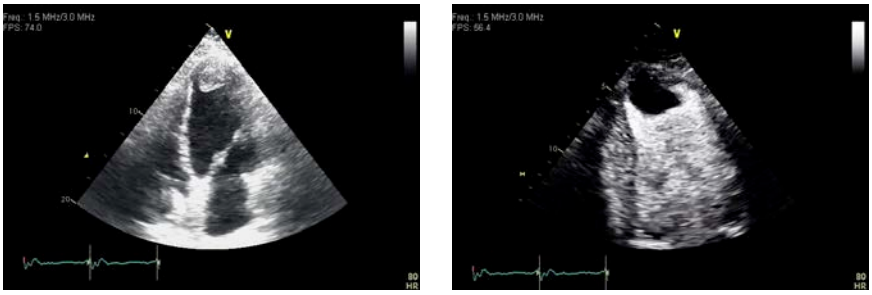
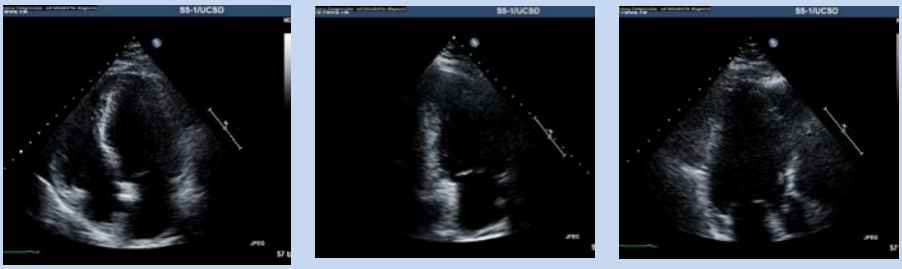


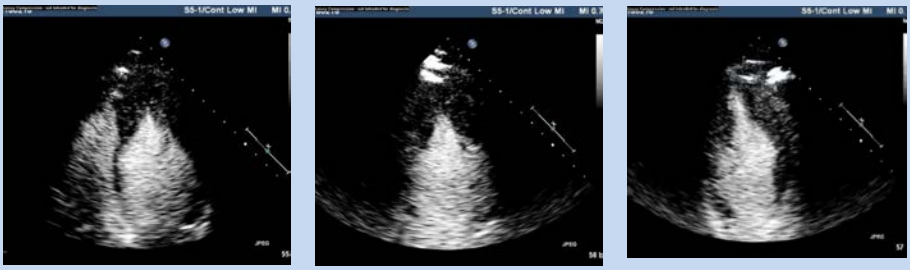
84

54 YO male with abnormal ECG



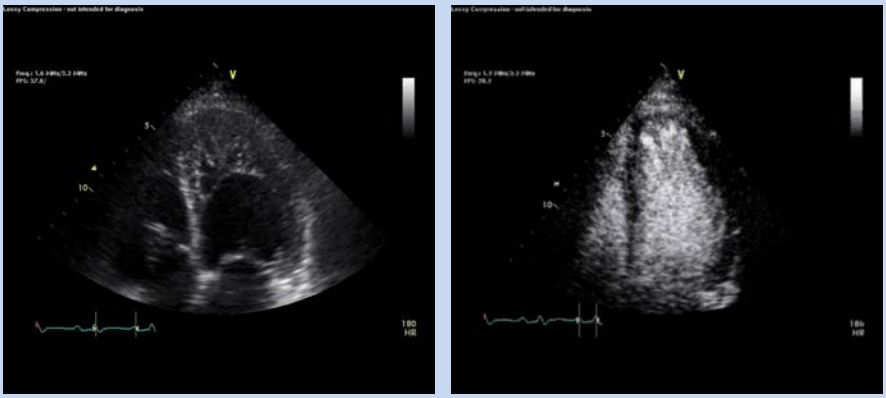
90

54 yo male with abnormal ECG and apical HCM



92

Contrast for Non-Compaction



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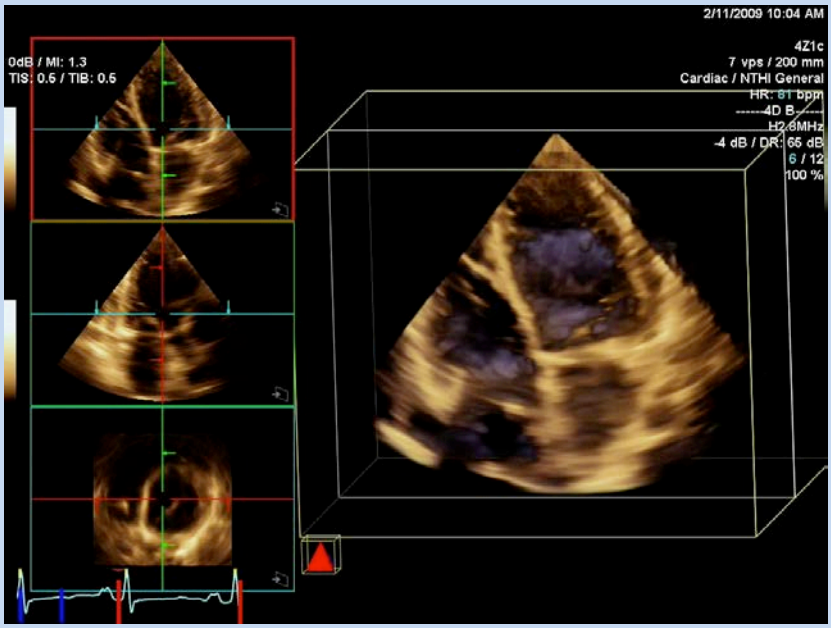
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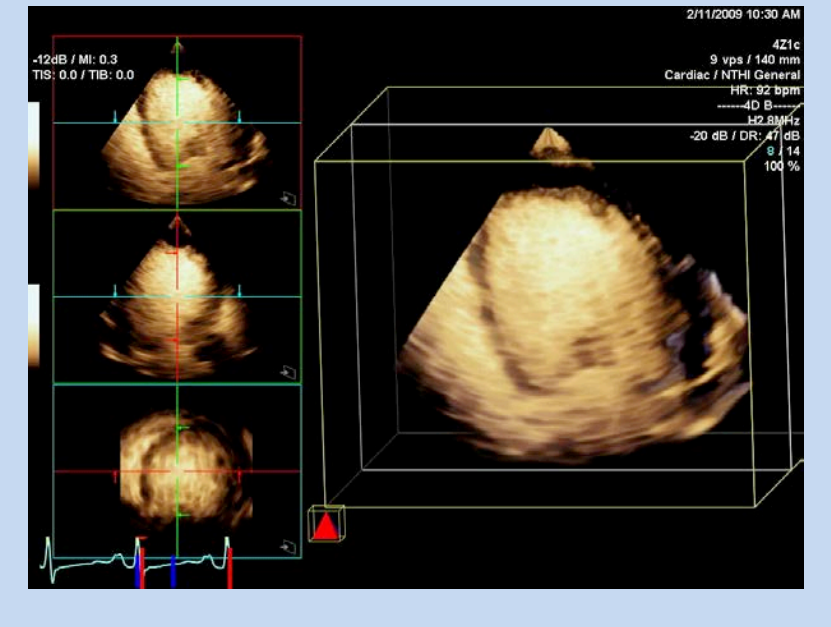
4Z1c
7 vps / 200 mm
Cardiac / NTHI General
HR: 81 bpm
4D B
H2.6MHz
-4 dB / DR: 65 dB
6 / 12
100 %
0dB / MI: 1.3
TIS: 0.5 / TIB: 0.5

99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9 vps / 140 mm
Cardiac / NTHI General
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9 / 14
100 %
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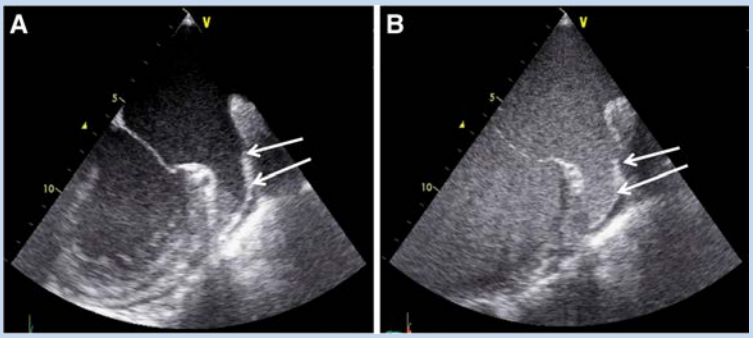
TIS: 0.0 / TIB: 0.0

101

Contrast TEE for LAA



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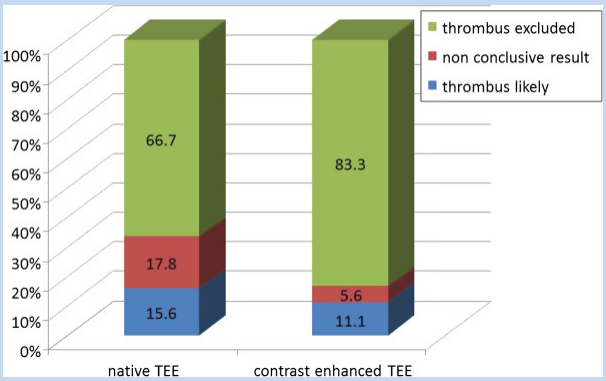
Contrast TEE for LAA



Jung et al; Cardiovasc Ultrasound, 2013

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Hypertrabeculation/Noncompaction: Background

- The LV normally has few trabeculae
- The phenotype of hypertrabeculation (HTB) may be seen in a varienty of conditions
  - ***Noncompaction Cardiomyopathy*** and others
- Dilated cardiomyopathy often results in HTB
- Contrast echo well suited to identify HTB
- We studied the prevalence, magnitude, and significance of HTB in DCM

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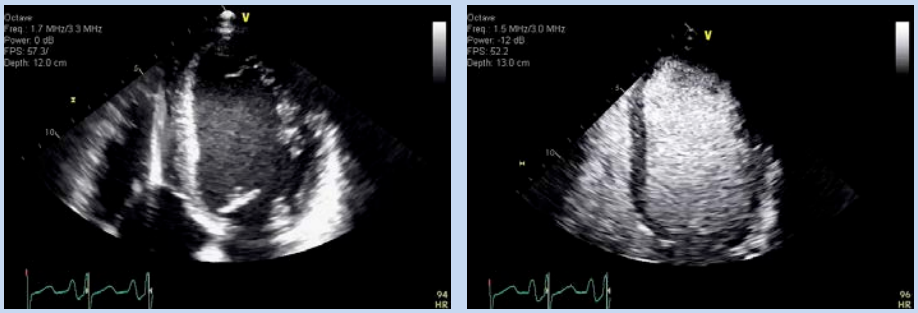

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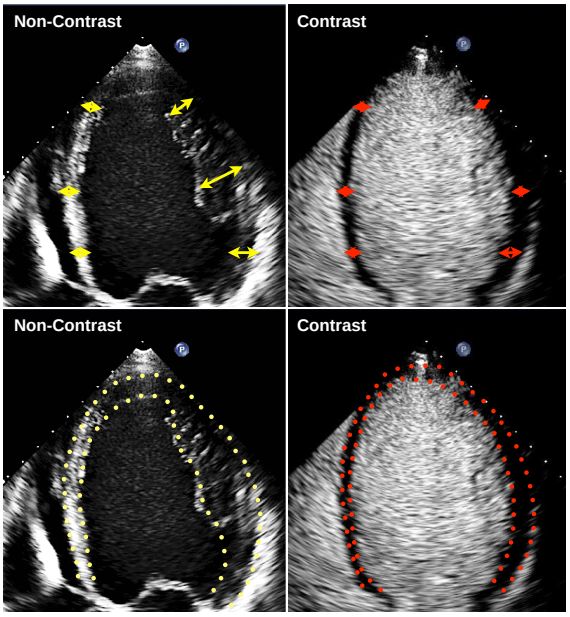
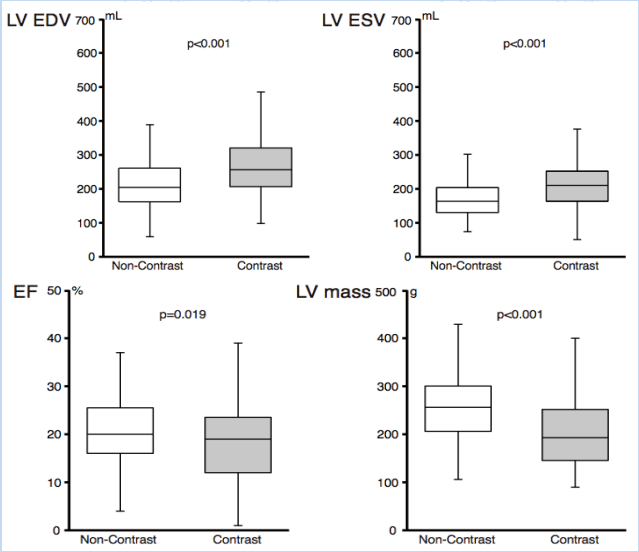


129

LV Size/Function: Con vs Non



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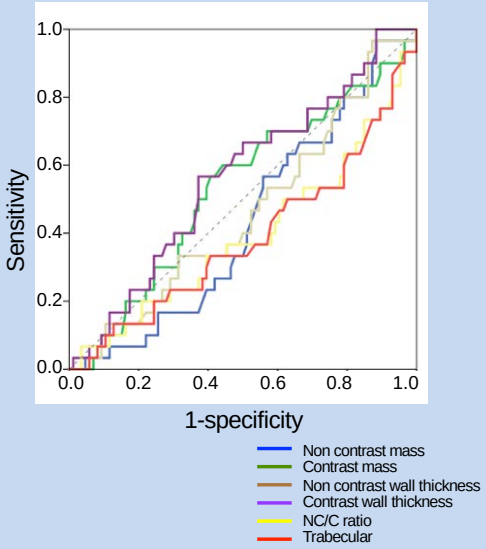
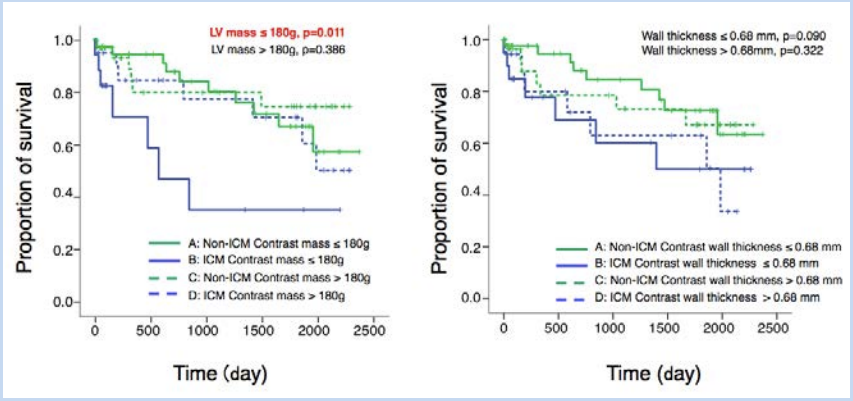
ROC curve - All Cause Mortality

Parameters	AUC
Non contrast mass	0.432
Contrast mass (cut off value=180g)	0.532
Non contrast LV wall thickness	0.462
Contrast LV wall thickness (cut off value=0.68mm)	0.564
NC-mass/C mass ratio	0.392
Trabecular	0.384



134

Kaplan-Meier survival for Non-ICM and ICM



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Hypertrabeculation (HTB): Conclusions

- HTB is prevalent in DCM (60%)
  - Apical-lateral segments are most involved
- Compacted myocardium yields increased volumes but decreased EF
- Compacted myocardium yields superior sensitivity/specificity for all cause mortality
  - Greater influence in ICM
- Delineation of compacted myocardium by contrast may be of value in DCM patients.

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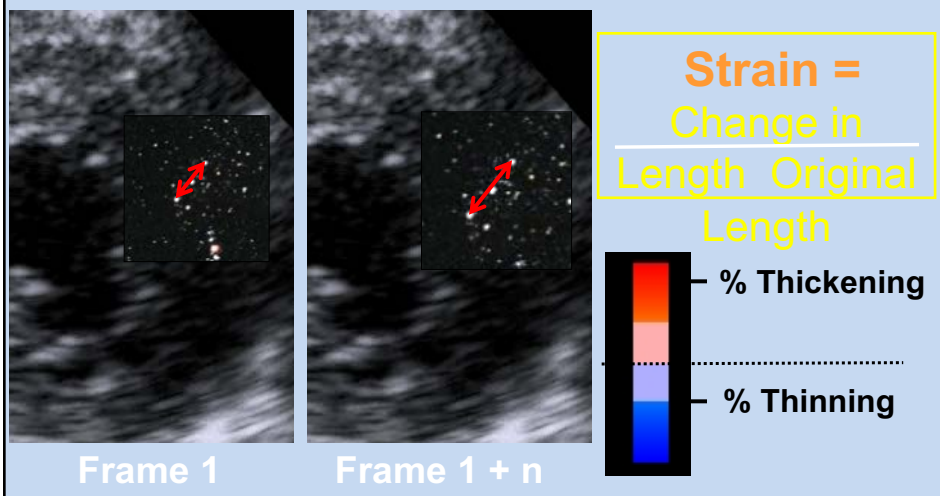
Calculation of Strain From Speckle Tracking



Modified from Freedman Z. and Lysysanksyv P

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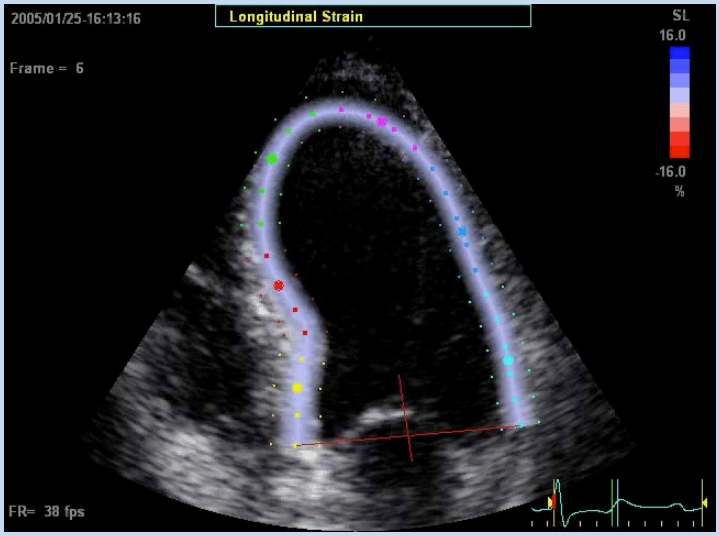

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Applications of Strain Measures

- Detection of LV dysfunction
  - Especially with normal EF
- Assessment of prognosis in heart failure
- Detection of cardiotoxicity with chemotherapy
- Diagnosis of amyloidosis
- Assessment of cardiomyopathy (HCM)
- Assessment of aortic stenosis
- Evaluation of hypertrophy, hypertension, athletes
- Detection of myocardial ischemia

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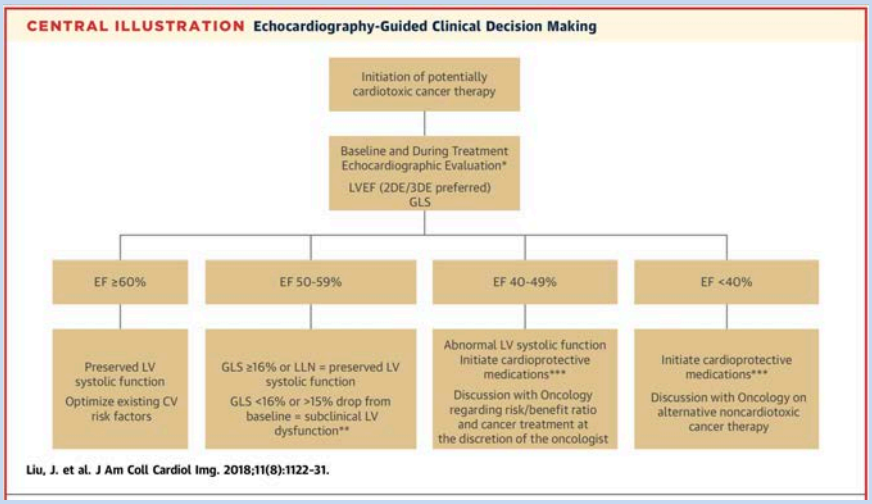

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Intraventricular Flow: Background

- Intraventricular flow (IVF) may contain important data in pts with cardiac disease
- Doppler enables assessment of IVF
- Metrics are needed to quantify IVF
- Goal to develop metrics for Doppler IVF
- Goal to apply metrics to study IVF DCM and predict thrombosis

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Applications of Flow Visualization

- Normal hemodynamic performance
- Dilated cardiomyopathy
- Abnormal conduction, pacemakers
- Prosthetic valves
- Shunts
- Regurgitant/stenotic valves
- RV and LA flow
- Aorta and peripheral vessels

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VORTICITY (VORTEX FORMATION)

- ***Vorticity***: a property of a fluid particle based on its local angular velocity that describes its tendency to rotate.
- A ***vortex*** is, therefore, a circular or elliptical-shaped rotating mass of fluid spinning around a virtual central axis
  - Size
  - Flow intensity
  - Position

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Effect of Vortices

- Preserves momentum by maintaining the motion of blood inside cardiac chambers
  - Prevents stasis
- Avoids excessive dissipation of energy, facilitating inflow into the ventricle
  - Conserves kinetic ener
- Redirects flow towards the LVOT and aortic valve
  - Facilitates ejection of blood

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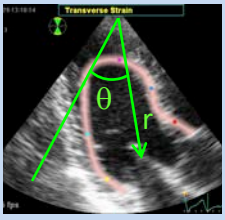
2D color Doppler velocimetry (echo-CDV)

Conventional acquisition

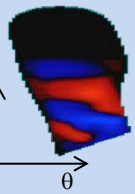
2D Continuity equation
- neglect through-plane fluxes
- Impermeability at the walls

$$\partial_\theta V_\theta = -r\partial_r V_r - V_r$$

2D Color Doppler

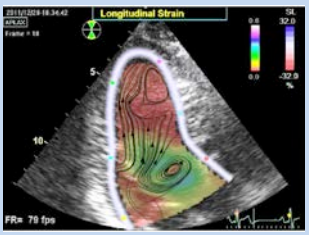


B-Mode Wall Tracking



$V_\theta(r,\theta)$

2D flow map overlaid on anatomical image



Garcia, del Alamo *et al*, *IEEE Trans Med Imag*. 2010

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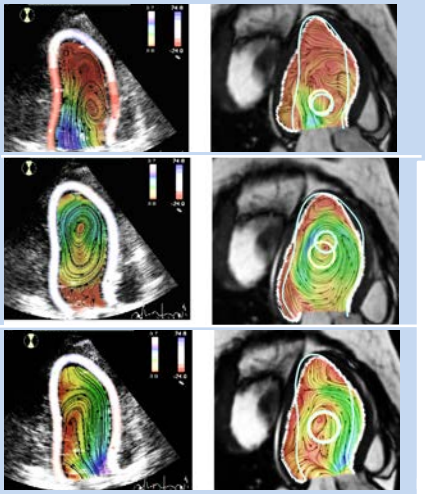
Validation: Echo-CDV vs Phase Contrast MRI

2D+t Doppler | Phase Contrast MRI



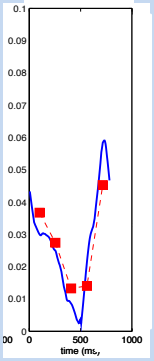
Vortex properties

(N=17 volunteers, 85 frames)

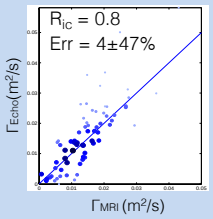
2D+t Doppler

Phase Contrast MRI

Circulation



Vortex circulation



Bermejo *et al*, *Am J Physiology* 2014

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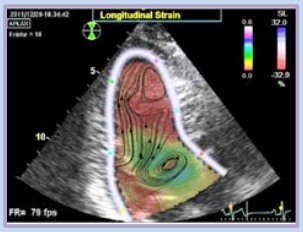
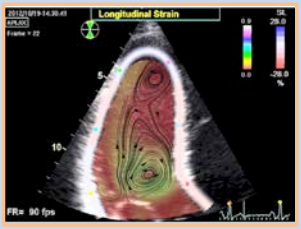
Reproducibility of echo-CDV

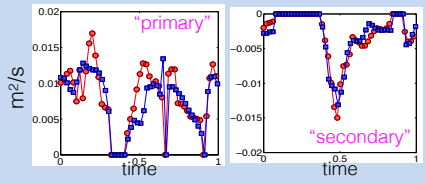
- Madrid, Spain (Dec 2011). Heart Rate 51
- Hospital Gregorio Maranon, GE Vivid 7
- Sonographer had extensive experience with 2D+t acquisition protocol

- San Diego, CA (Oct 2012). Heart Rate 50
- UCSD Hillcrest Medical Center, GE Vivid 9
- Sonographer had **no** previous experience with 2D+t acquisition protocol

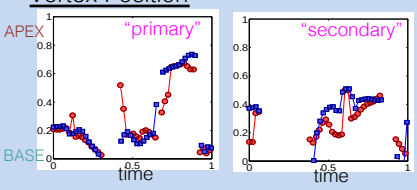




Vortex Circulation



Vortex Position



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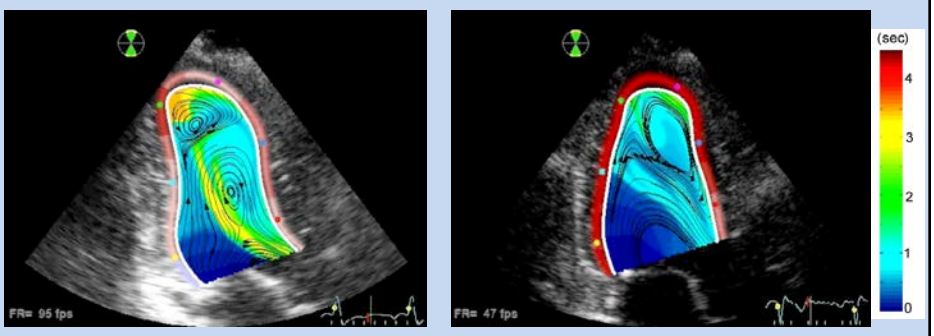
Early Data

Residence Time
Patient with cardiomyopathy

Residence Time
Normal LV function subject



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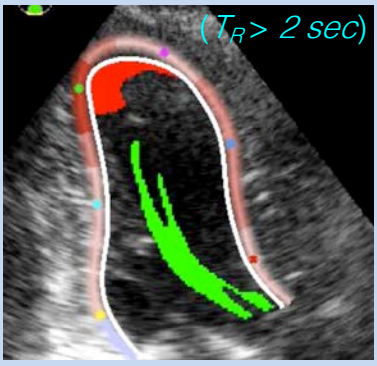
Applied Analysis

Segment residual volumes

- Do not mix with incoming blood
- Are not ejected during systole
- These regions should be at high stasis risk



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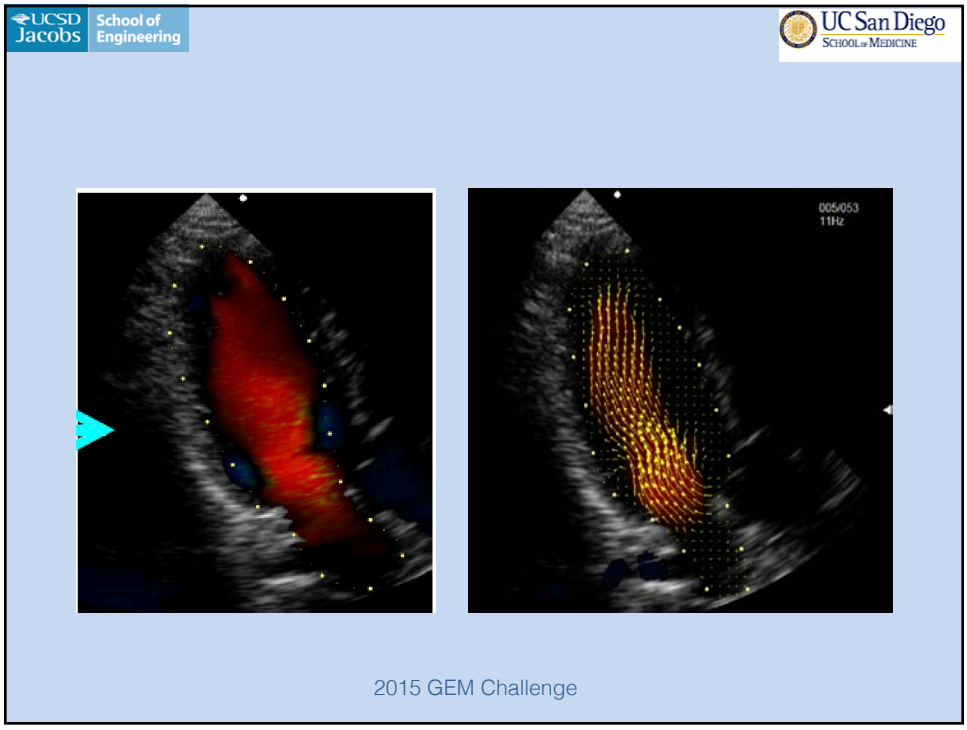
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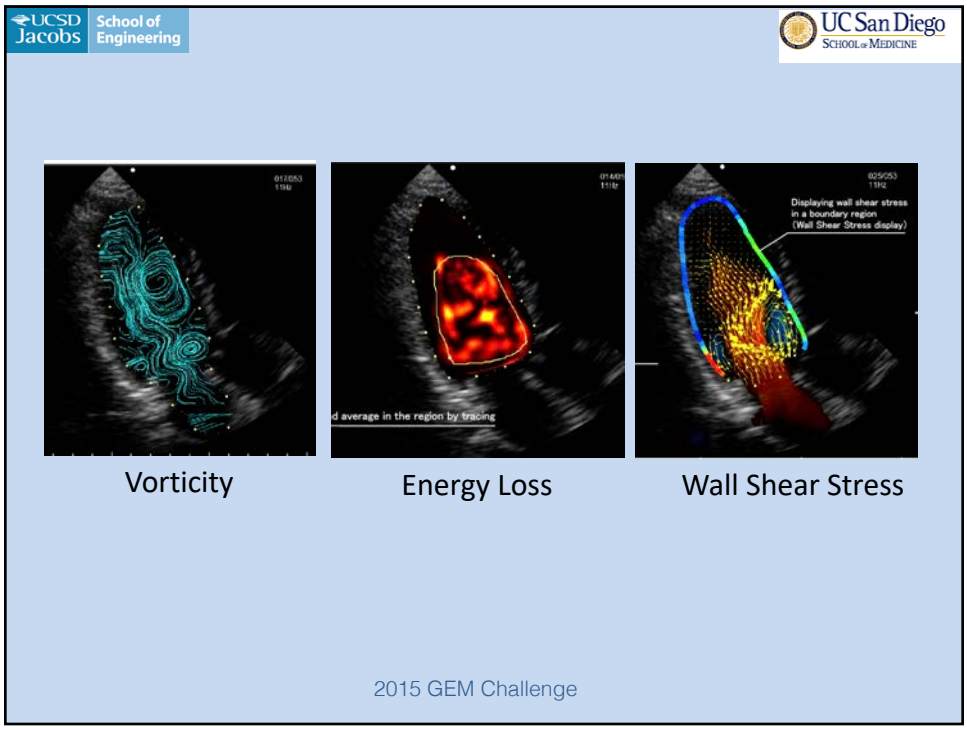
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Displaying wall shear stress in a boundary region (Wall Shear Stress display)
Vorticity
Energy Loss
Wall Shear Stress
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Intraventricular Flow Visualization

- The technique is in its infancy
- Echo is the most feasible method for study
  - Color Doppler vs contrast PVI
- Quantitative metrics are being developed
- Can provide data on (patho) physiology
- Clinical applications are evolving
- Risk of thrombus may change clinical practice

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Handheld or Pocket or Point of Care Echocardiography

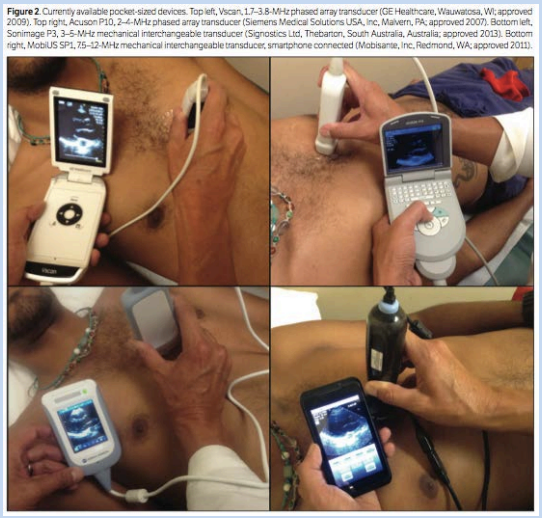

Figure 2. Currently available pocket-sized devices. Top left, Vscan, 1.7–3.8-MHz phased array transducer (GE Healthcare, Wauwatosa, WI; approved 2009). Top right, Acuson P10, 2–4-MHz phased array transducer (Siemens Medical Solutions USA, Inc, Malvern, PA; approved 2007). Bottom left, Sonimage P3, 3–5-MHz mechanical interchangeable transducer (Signostics Ltd, Thebarton, South Australia, Australia; approved 2013). Bottom right, MobiUS SP1, 75–12-MHz mechanical interchangeable transducer, smartphone connected (Mobisante, Inc, Redmond, WA; approved 2011).

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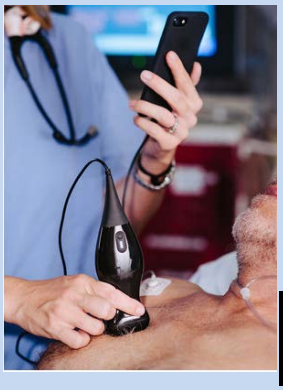
New "Ultrasound on a Chip could Revolutionize Medical Imaging



Exiting handheld require piezoelectric technology and require multiple probes to bring the price between 8k to 15k. Replace piezocrystals with a micromachine that acts like a drum to generate vibrations The voltage bouncing back from the body is registered as an electrical signal which creates the image

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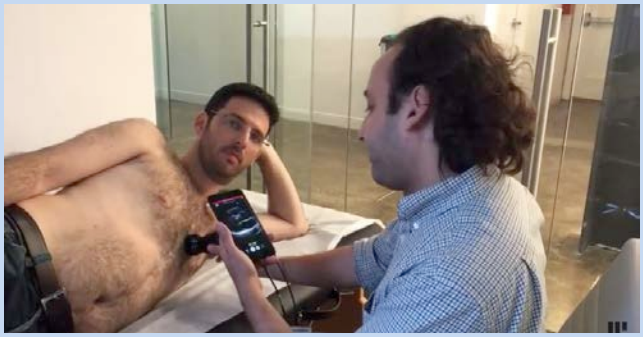
Automated Intelligence. ECHO *GPS*



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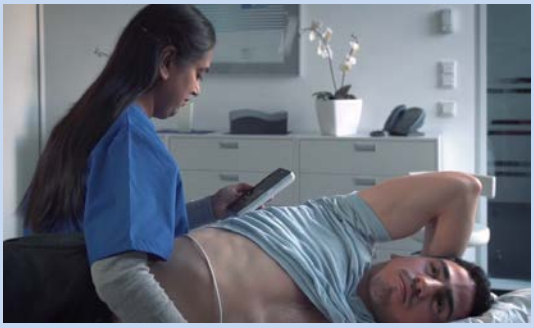
LVIVO™ EF on GE Healthcare's VSCAN Extend ultrasound

LVIVO EF has already been implemented on GE Healthcare's VSCAN Extend ultrasound,



CLICK FOR VIDEO

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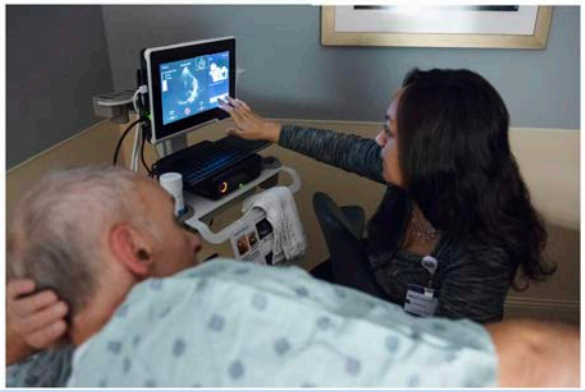
CMAs use Bay Labs AI to capture cardiac ultrasound images at Northwestern Medicine during SHAPE study

*SHAPE: Seeing the Heart with AI Powered Echo" is study to evaluate the use of **AI-guided cardiac ultrasound** to enable medical professionals with no prior scanning experience to capture high-quality echocardiograms.

BAYLABS



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Applications of Handheld Echo

- Emergency imaging
- Limited exams
- Extended physical examination
  - the "ultrasonic stethoscope"

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Laennec invented the stethoscope, the original employment of the instrument being his desire to save a young woman's modesty from the shock of having him listen directly to her chest.

161

Accuracy of Current PE

- *St Clair* AnnIntMed 1992 63 res 50-60% error
  MR, AR, MS
- *Mangione* JAMA 1997 453 res 80% error
- *Roldan* AJC 1996 15 card 20% error
- *Jost* AmJMed 2000 20 card 21% error
- *March* MayoProc 2005 17 card 66% error
  All MDs had 76% error
- *Criley* ArchIntMed 2006 860 MDs 42% error
  Cards fellows best at 30% error
  No difference for intern to faculty

Functional murmurs

162

"ULTRASOUND STETHESCOPE": LVEF EXAMPLE

- Physical exam limited in assessing EF
- Echo gives good visual EF estimate
- Echo exam of LV may be easier to master than physical exam
- Echo can provide directional changes
- Echo improves LV assessment by medical residents (Kimura et al)

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Usefulness of a Hand-Held Ultrasound Device for Bedside Examination of Left Ventricular Function

Bruce J. Kimura, MD, Stan A. Amundson, MD, Casey L. Willis, RDCS, Elizabeth A. Gilpin, MS, and Anthony N. DeMaria, MD

The central role of physical examination in detecting cardiovascular disorders is attributable to its low cost and ease of application despite reported limitations in accuracy.[1-3] The recent development of inexpensive hand-held ultrasound devices will potentially allow the incorporation of ultrasound into the routine bedside examination and thereby improve diagnostic accuracy.[4] Patients with left ventricular (LV) systolic dysfunction represent a group who can benefit from early detection and treatment,[5,6] but in whom the condition may be asymptomatic[7,8] and elude physical diagnosis. The present study was undertaken to examine whether physicians who undergo brief training in the use of a hand-held ultrasound device can improve their capability to diagnose patients with significant LV dysfunction.

...

The study took place at an accredited teaching hospital using second- and third-year internal medicine residents (n = 13). All residents initially received a 1-hour review lecture on the use of physical examination techniques to detect impaired LV systolic function.[2] Within the same month, a 1-hour ultrasound training session was given including instruction on proper orientation of the parasternal long-axis view, echocardiogram, review of videotaped examples of normal and abnormal systolic function, and a "hands-on" exercise for each resident to image and interpret findings on 5 normal volunteers using a 7-pound, hand-carried ultrasound device with a 2.5-MHz transducer probe (OptiGo, Philips Medical Systems, Andover, Massachusetts). Residents were instructed to evaluate impaired systolic function based upon 3 echocardiographic criteria: (1) presence of abnormal wall motion or thickening, (2) inability of the mitral valve to open fully and nearly touch the septum (i.e., the E-point septal separation distance of >1 cm), and (3) failure of the midventricle to become smaller than the base of the heart.

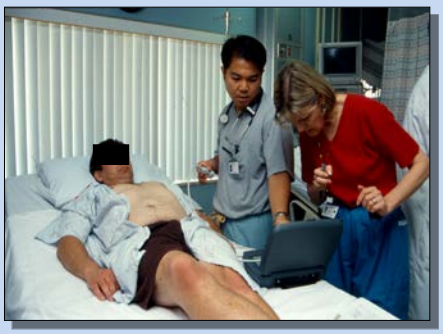
Six weeks later, residents were formally evaluated in their examination of 12 model patients for the presence of significant LV systolic dysfunction. Five volunteer patients with a history of an LV ejection fraction <50% and asymptomatic with medical therapy were age-matched to 7 patients or normal volunteers with ejection fractions ≥60%. No model had undergone thoracotomy, had significant valvular disease, had pacer or defibrillator placement, or was recently admitted to the hospital or had contact with any resident physician. All 12 models underwent measurement of ejection fraction by Simpson's rule,[9] performed by experienced sonographers using a standard echocardiographic instrument (Sonos 5500, Philips Medical Systems). An adequate-quality parasternal long-axis image was obtained for each patient and reviewed by a cardiologist (BJK) for the presence of the 3 echocardiographic criteria of LV dysfunction. Immediately after echo evaluation, a senior faculty internist (SAA), blinded to the results of the echocardiogram, physically examined each model.

Residents were initially given 5 minutes to perform a physical examination to detect LV dysfunction. No significant verbal communication was allowed. The physical diagnosis was then scored as: 1 = definitely normal, 2 = probably normal, 3 = equivocal, 4 = probably abnormal, and 5 = definitely abnormal. Immediately after the physical examination, the resident performed a 3-minute ultrasound examination. The quality of the best image obtained during the ultrasound examination was scored on a 4-point scale by the proctor: 0 = no image, 1 = only motion seen with visualization of any 1 of 3 landmarks of the parasternal long-axis view (the aortic valve, mitral valve, and LV long axis), 2 = any 2 of the 3 landmarks present, and 3 = all 3 landmarks present. An additional point was given if endocardial definition was near complete. A total quality score of 3 or 4 was considered an adequate study. After obtaining the ultrasound, the resident physician was given the opportunity to revise his/her diagnostic score based on all the data assimilated through physical and ultrasonic examination of the model. This was considered the final diagnostic score.

Initial diagnostic error (after physical examination), quantified as the absolute difference between the true status of the patient (1 = normal, 5 = abnormal) and the initial diagnostic score, was calculated for each resident for each patient. Similarly, the final diagnostic error (after ultrasound examination) was calculated from the final diagnostic score. The initial diagnostic error was then subtracted from the final diagnostic error so that a negative difference would indicate an improved, and a positive difference a worsened, diagnostic error. Patient evaluations showing improvement, no change, or worsening of the diagnostic error after the use of the hand-held ultrasound device were scored −1, 0, or +1, respectively.

From the Department of Cardiology, Scripps Mercy Medical Center, San Diego; and the Department of Cardiology, University of California, San Diego, San Diego, California. Dr. Kimura is supported in part by an unrestricted grant from Philips Medical Systems, Andover, Massachusetts. Dr. Kimura's address is: University of California, San Diego, Scripps Mercy Nonnewaine Cardiology, 230 Prospect Place #250, Coronado, California 92118. Email: kimura.bruce@scrippshealth.org. Manuscript received March 19, 2002; revised manuscript received and accepted June 21, 2002.

The American Journal of Cardiology Vol. 90 November 1, 2002



- 2 sessions echo training: Low EF
- 10/13 residents improved diagnosis in 12 patients (5 low EF; 7 nls)
- >80% exams of fair or good quality.

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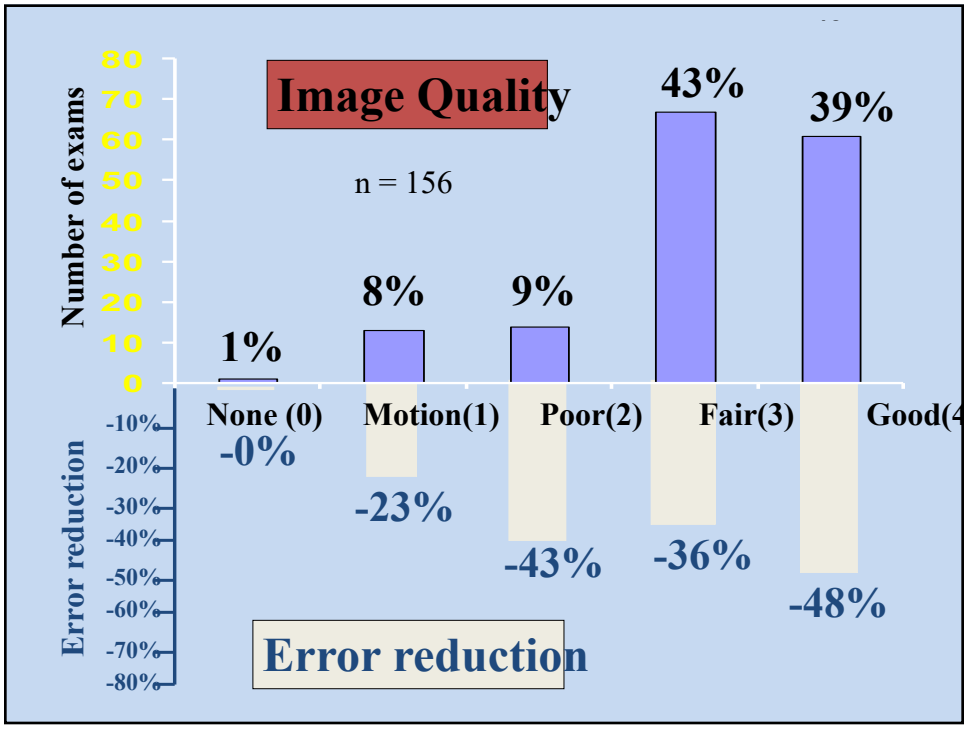

165

Conclusion:

•These findings suggest that a briefly-trained physician can perform a simplified bedside ultrasound exam using a hand-held device to improve detection of LV systolic dysfunction.

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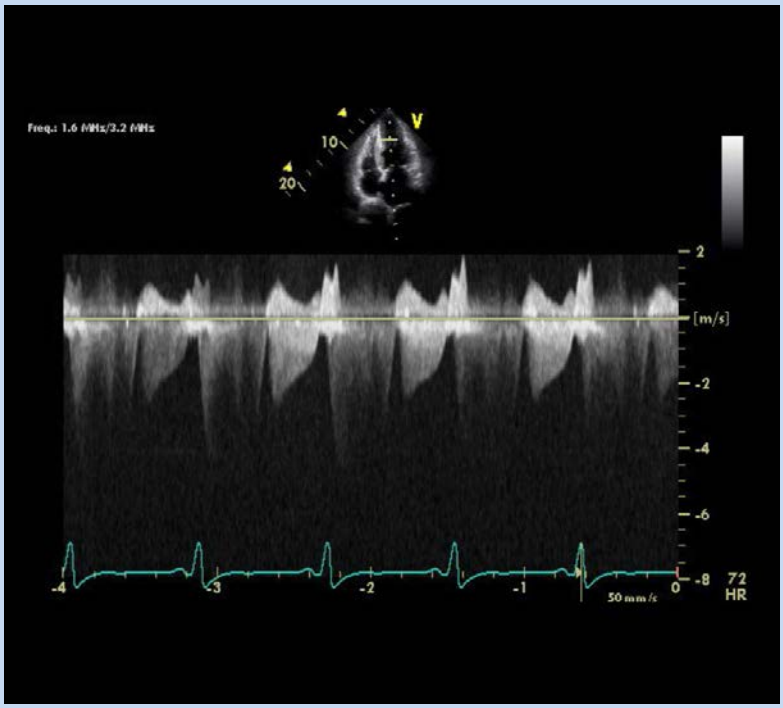
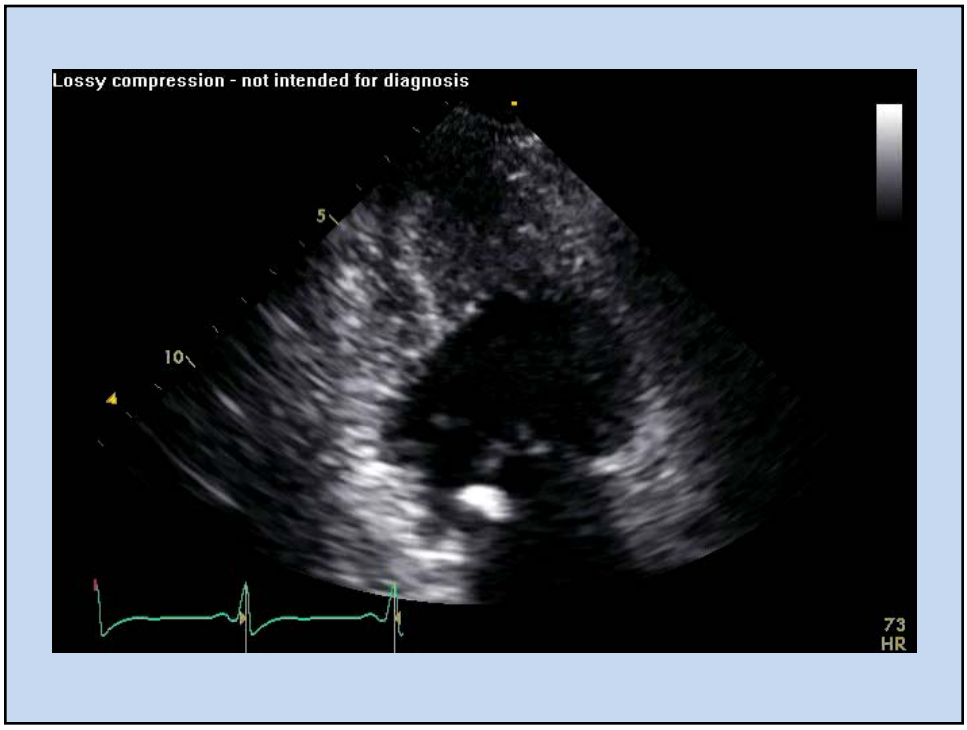


168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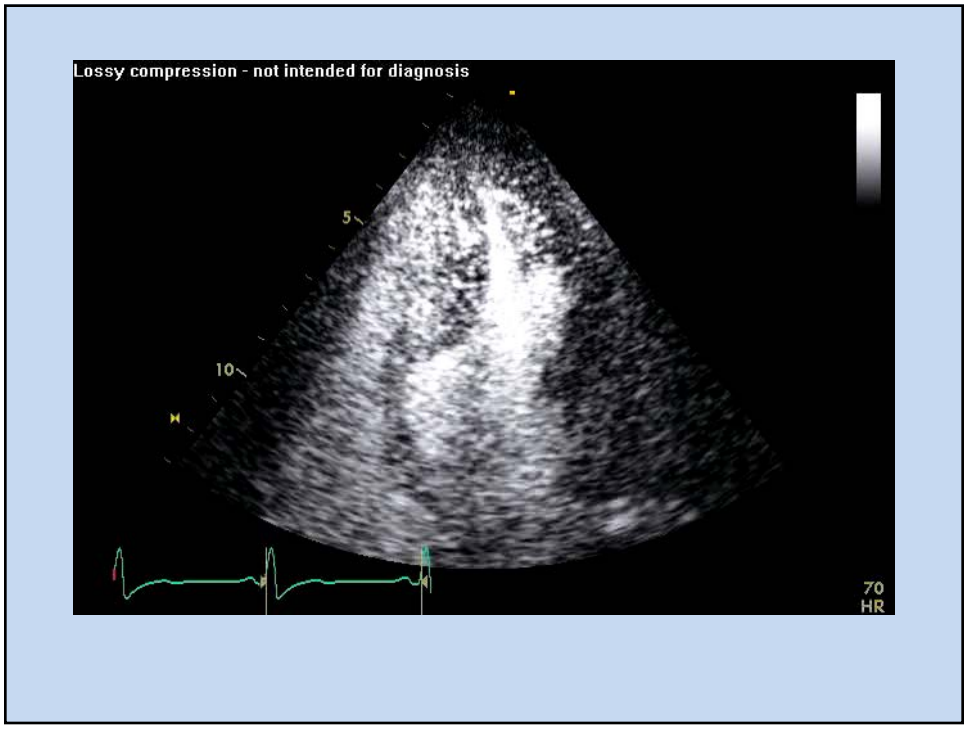
5
10
73
HR

177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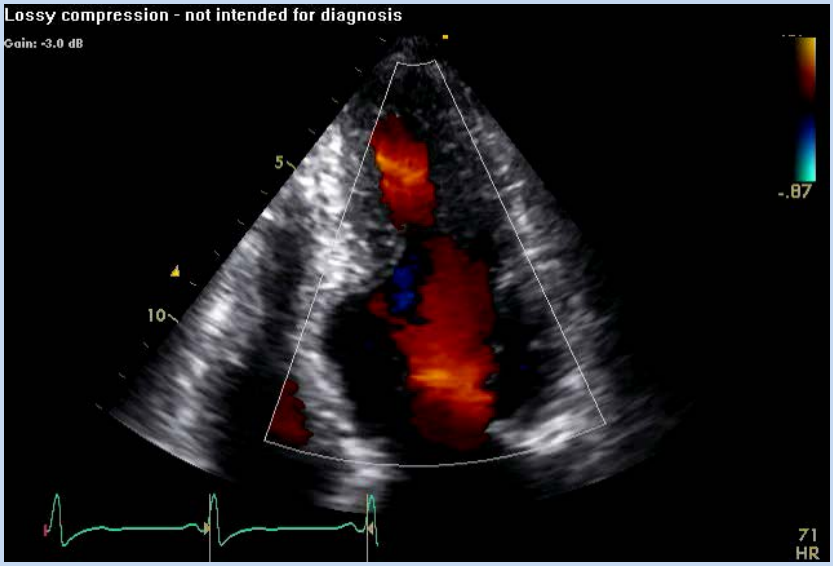

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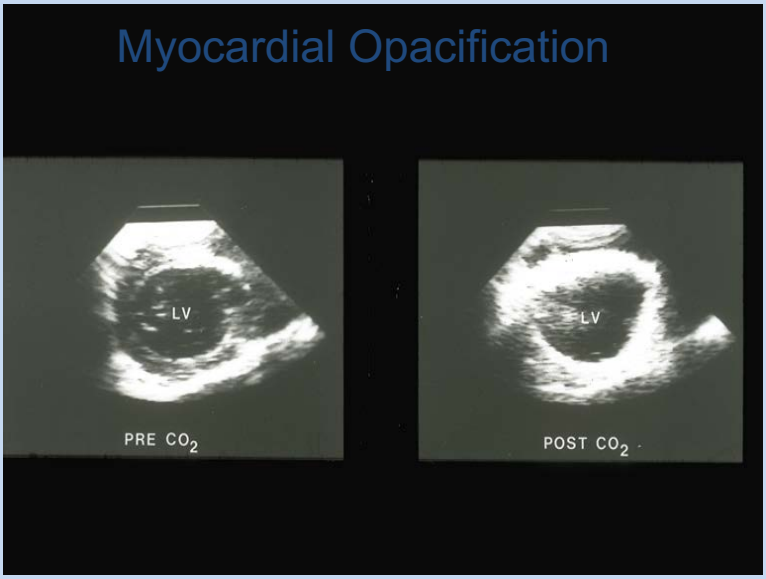
Myocardial Opacification



DeMaria, Bommer et al. Circ Suppl: 1979

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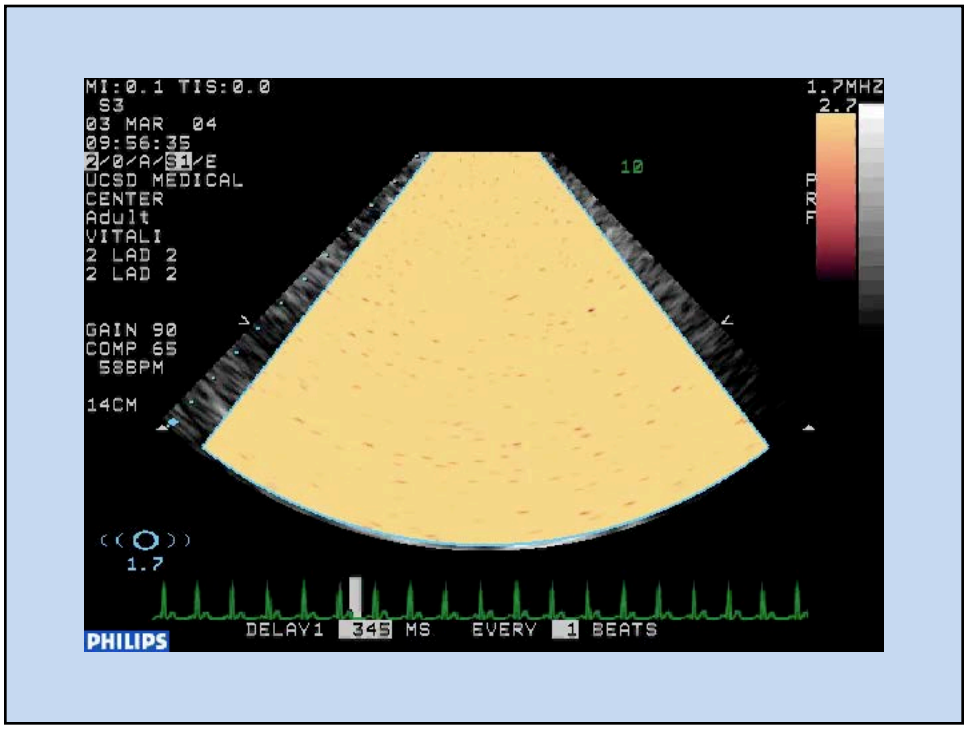
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PHILIPS

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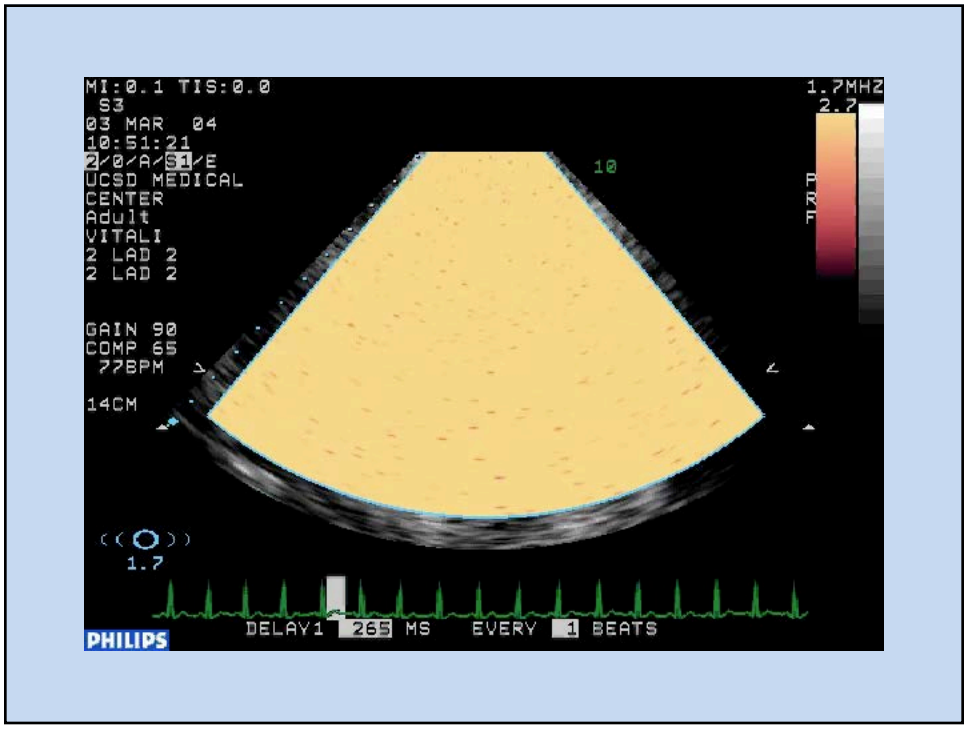
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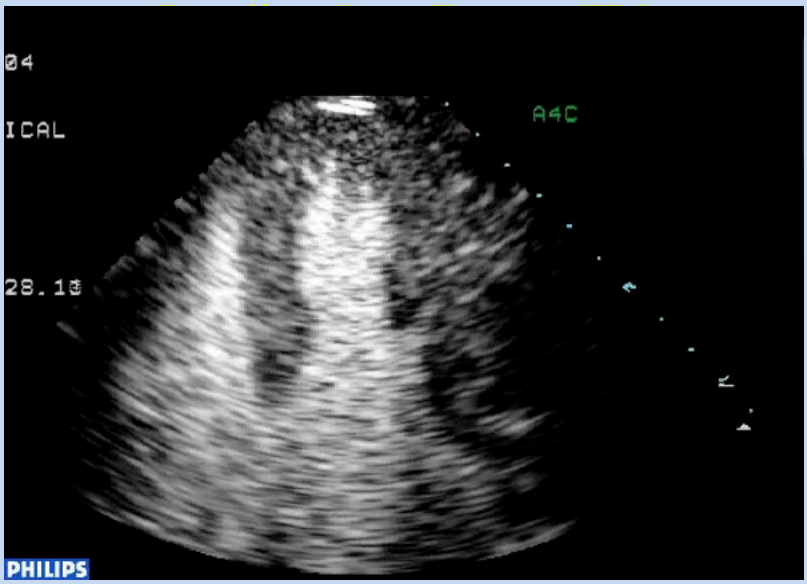
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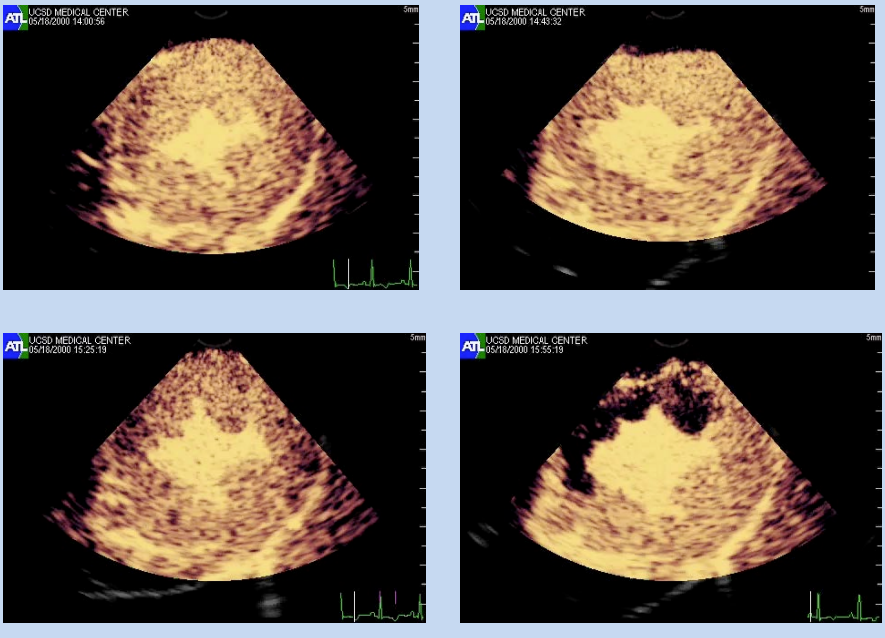
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European Journal of Echocardiography (2009) 10, 26–35
doi:10.1093/ejechocard/jen321

CLINICAL/ORIGINAL PAPER

Detection of coronary artery disease with perfusion stress echocardiography using a novel ultrasound imaging agent: two Phase 3 international trials in comparison with radionuclide perfusion imaging

Roxy Senior[1]*, Mark Monaghan[2], Michael L. Main[3], Jose L. Zamorano[4], Klaus Tiemann[5], Luciano Agati[6], Neil J. Weissman[7], Allan L. Klein[8], Thomas H. Marwick[9], Masood Ahmad[10], Anthony N. DeMaria[11], Miguel Zabalgoitia[12], Harald Becher[13], Sanjiv Kaul[14], James E. Udelson[15], Frans J. Wackers[16], Richard C. Walovitch[17], and Michael H. Picard[18], for the RAMP-1 and RAMP-2 Investigators

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RAMP 1 and 2

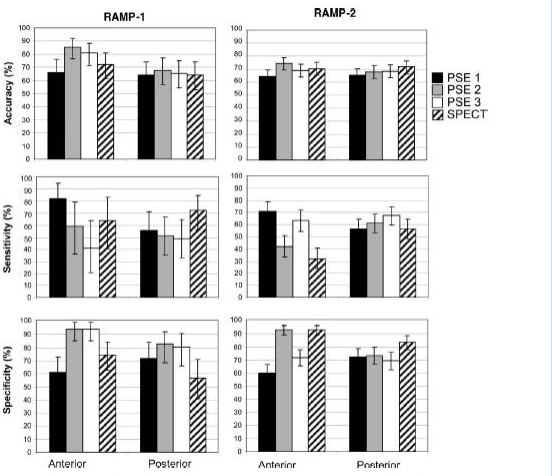

Figure 4 Defect detection and localization by vascular territory. Accuracy, sensitivity, and specificity among PSE and SPECT readers in the detection of coronary artery disease in anterior (LAD) and posterior (RCA and LCx) circulation.

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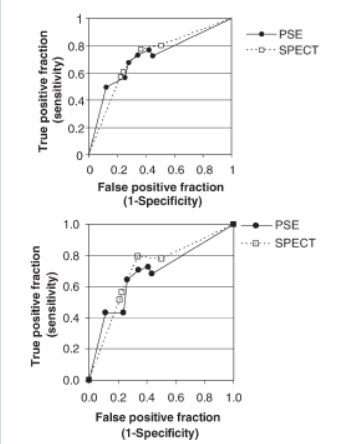
ROC Analysis: RAMP 1 and 2



Senior et al: Eur J Echo; 2009

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Comparison of Sulfur Hexafluoride Microbubble (SonoVue)-Enhanced Myocardial Contrast Echocardiography With Gated Single-Photon Emission Computed Tomography for Detection of Significant Coronary Artery Disease

A Large European Multicenter Study

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London, Harrow, United Kingdom; Milan, Parma, Rome, Monza, Genoa, Bari, and Pavia, Italy; Münster and Mainz, Germany; Edegem, Belgium; Corbeil-Essonnes and Paris, France; Barcelona, Spain; Edmonton, Alberta, Canada; Rotterdam, the Netherlands; Athens, Greece; and Łódź, Poland

Objectives The purpose of this study was to compare sulfur hexafluoride microbubble (SonoVue)-enhanced myocardial contrast echocardiography (MCE) with single-photon emission computed tomography (SPECT) relative to coronary angiography (CA) for assessment of coronary artery disease (CAD).

Background Small-scale studies have shown that myocardial perfusion assessed by SonoVue-enhanced MCE is a viable alternative to SPECT for CAD assessment. However, large multicenter studies are lacking.

Methods Patients referred for myocardial ischemia testing at 34 centers underwent rest/vasodilator SonoVue-enhanced flash-replenishment MCE, standard ^{99m}Tc-labeled electrocardiography-gated SPECT, and quantitative CA within 1 month. Myocardial ischemia assessments by 3 independent, blinded readers for MCE and 3 readers for SPECT were collapsed into 1 diagnosis per patient per technique and were compared to CA (reference standard) read by 1 independent blinded reader.

Results Of 628 enrolled patients who received SonoVue (71% males; mean age: 64 years; >1 cardiovascular [CV] risk factor in 99% of patients) 516 patients underwent all 3 examinations, of whom 161 (31.2%) had ≥70% stenosis (131 had single-vessel disease [SVD]; 30 had multivessel disease), and 310 (60.1%) had ≥50% stenosis. Higher sensitivity was obtained with MCE than with SPECT (75.2% vs. 49.1%, respectively; $p < 0.0001$), although specificity was lower (52.4% vs. 80.6%, respectively; $p < 0.0001$) for ≥70% stenosis. Similar findings were obtained for patients with ≥50% stenosis. Sensitivity levels for detection of SVD and proximal disease for ≥70% stenosis were higher for MCE (72.5% vs. 42.7%, respectively; $p < 0.0001$; 80% vs. 58%, respectively; $p = 0.005$, respectively).

Conclusions SonoVue-enhanced MCE demonstrated superior sensitivity but lower specificity for detection of CAD compared to SPECT in a population with a high incidence of CV risk factors and intermediate-high prevalence of CAD. (A phase III study to compare SonoVue® enhanced myocardial echocardiography [MCE] to single photon emission computerized tomography [ECG-GATED SPECT], at rest and at peak of low-dose Dipyridamole stress test, in the assessment of significant coronary artery disease [CAD] in patients with suspect or known CAD using Coronary Angiography as Gold Standard–SonoVue MCE vs SPECT; EUCTR2007-003492-39-GR) (J Am Coll Cardiol 2013;62:1353–61) © 2013 by the American College of Cardiology Foundation

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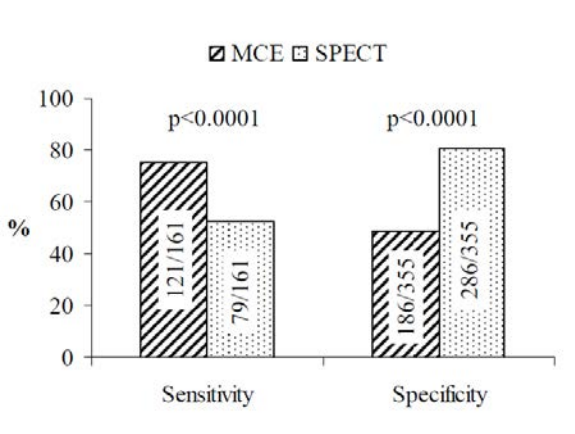
Diagnostic Accuracy: MCE vs SPECT



Senior et al; JACC, 2013

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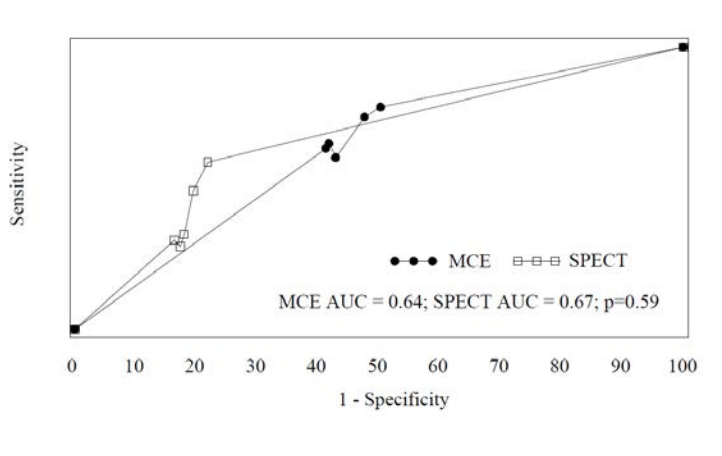
ROC Analysis: MCE vs SPECT



Senior et al; JACC, 2013

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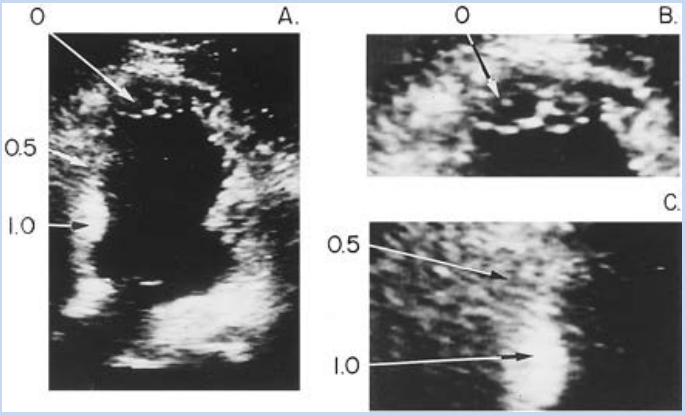
Viability by MCE



Ragosta et al; , 89:1994

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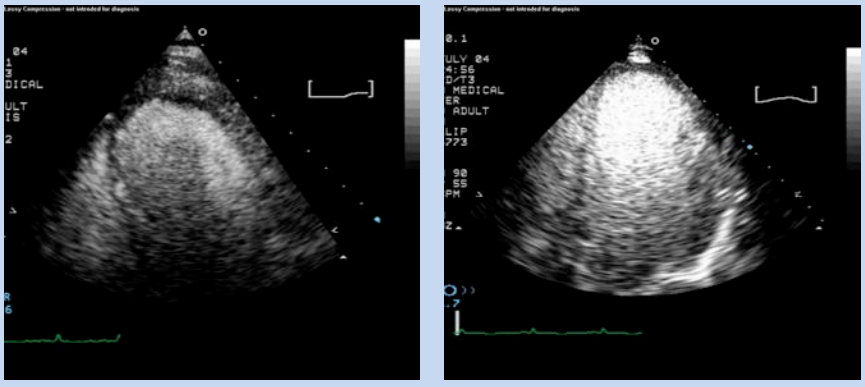

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MCE for Myocardial Viability Post MI

Authors	Imaging type	Sensitivity (%)	Specificity (%)	Pts
Janardhanan (2005)	Low MI	82	83	42
Hickman (2005)	Low MI	83	78	56
Senior (2003)	High MI	62	85	96
Greavea (2003)	Low MI	88	74	15
Aggeli (2003)	High MI	87	72	34
Janardhanan (2003)	Low MI	92	75	50
Hillia (2003)	Low MI	86	44	33
Hillis (2003)	High MI	80	67	38
Lepper (2002)	High MI	94	87	35
Main (2001)	Low MI	77	83	34
	Mean	83	75	(n 430)

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Myocardial contrast echocardiography has not yet achieved use as a *clinical tool*.

Why?

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Why is MCE Not Clinical?

- Images still inadequate in difficult patients
- Pulsing sequences still complex
- No agreed upon protocol exists
- Quantitation still has limited reproducibility
- Few multicenter studies are published
- No reimbursement

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Contrast-Enhanced Ultrasound Imaging of Intraplaque Neovascularization in Carotid Arteries

Correlation With Histology and Plaque Echogenicity

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Luigi Spagnoli, MD,‡ Roberto Chiesa, MD,* Domenico Cianflone, MD, FESC,*
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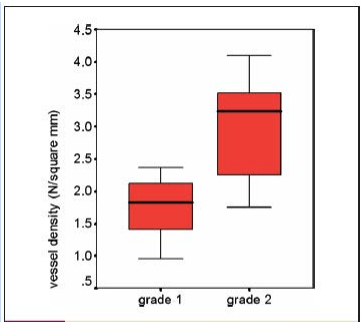

Figure 1 Vessel Density at Histology According to Plaque Contrast-Agent Enhancement

The density of vasa vasorum at histology (number per square millimeter) is greater in plaques with grade 2 contrast-agent enhancement at ultrasound imaging compared with those with grade 1.

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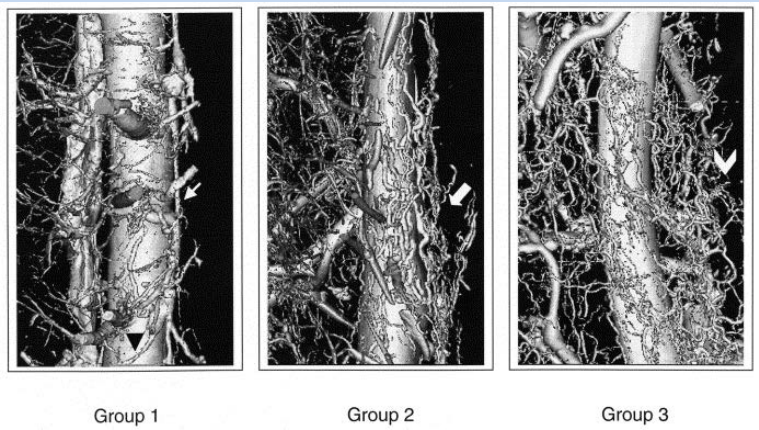
Vasa Vasorum



Herrmann et al. Circ Res; 2001

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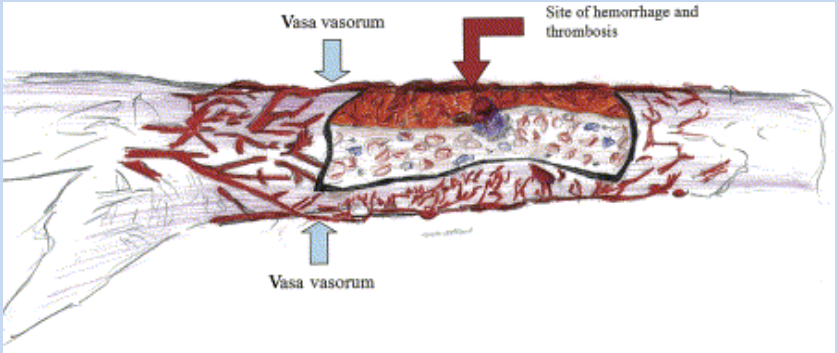
Vasa Vasorum



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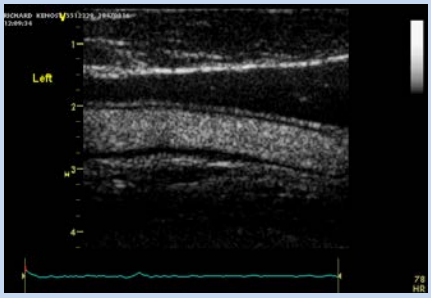
Contrast for Carotid Plaque



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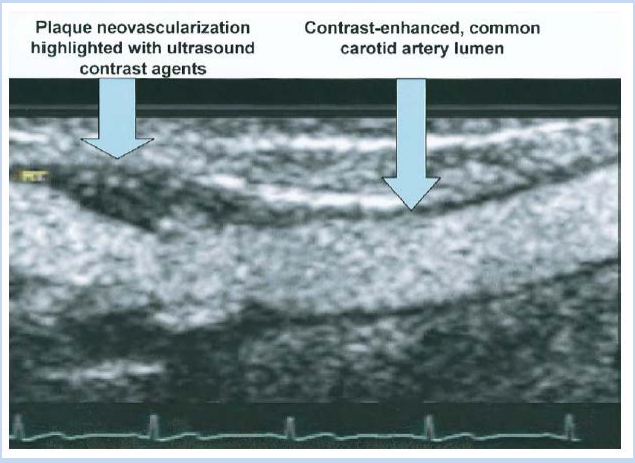
Contrast for Plaque Neovascularization



Feinstein et al; JACC, 2006

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Contrast Echo Other Than Border Definition

- Cardiac Shunts
- Doppler enhancement
- Cardiac Masses
  - Tumor vs Clot
- 3D enhancement
- Noncompaction
- Vascular enhancement

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68 year old man with long standing hypertension, COPD, chest pain, and a Grade II/VI ejection systolic murmur

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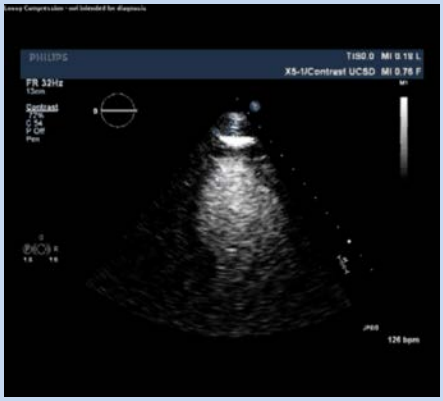
68 yo male with AS



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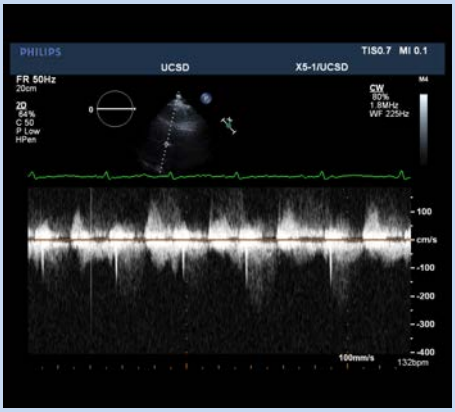
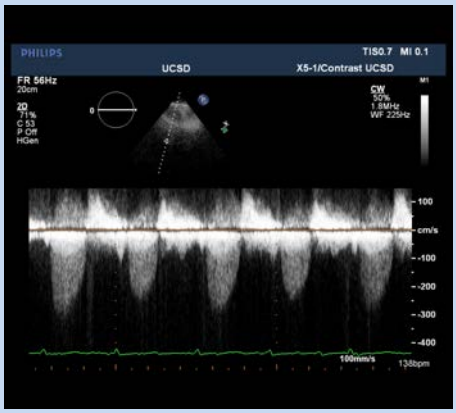
68 yo male with AS





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JACC Vol. 20, No. 4
October 1992:973–8

Clinical Application of Transpulmonary Contrast-Enhanced Doppler Technique in the Assessment of Severity of Aortic Stenosis

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Objective. The aim of this study was to demonstrate the clinical usefulness of the transpulmonary contrast-enhanced Doppler technique by using it to assess the severity of aortic stenosis.

Background. Sonicated albumin microbubbles can pass through the pulmonary circulation after peripheral venous injection and have been reported to enhance Doppler signals from the left side of the heart. Therefore, their use to determine aortic flow velocity would facilitate the assessment of the severity of aortic stenosis.

Methods. Twenty-two patients with aortic stenosis and seven normal volunteers were examined. Aortic flow velocity was recorded with continuous wave Doppler technique from an apical window before and after injection of 2 ml of sonicated albumin.

Results. In 10 patients with aortic stenosis, the aortic velocity envelope was too indistinct to determine the peak velocity before sonicated albumin was injected. After injection, the aortic flow Doppler signal was enhanced in 9 of the 10 patients and the velocity envelope became clear enough to measure the peak velocity, enabling calculation of the transaortic pressure gradient. In the remaining 12 patients with aortic stenosis and in all 7 normal volunteers, the velocity envelope was clear before injection and became much clearer after injection. The calculated transaortic pressure gradient showed a good agreement with catheterization measurements ($y = 1.1x - 6.5$, $r = 0.88$, $p < 0.001$, SEE = 16 mm Hg, $n = 13$). Duration of Doppler signal enhancement was measured as the time during which the envelope was clearer than before injection throughout the ejection period. The duration was significantly shorter in patients with aortic stenosis than in normal volunteers (16 ± 5 vs. 52 ± 32 s, $p < 0.01$). There was a significant correlation between left ventricular systolic pressure measured by catheterization and the duration of signal enhancement ($r = -0.69$), suggesting that albumin microbubbles were fragile at high pressure.

Conclusions. The transpulmonary contrast-enhanced Doppler technique using sonicated albumin is useful for assessing the severity of aortic stenosis even in patients with poor Doppler recordings, although the duration of signal enhancement might be affected by left ventricular systolic pressure.

(J Am Coll Cardiol 1992;20:973–8)

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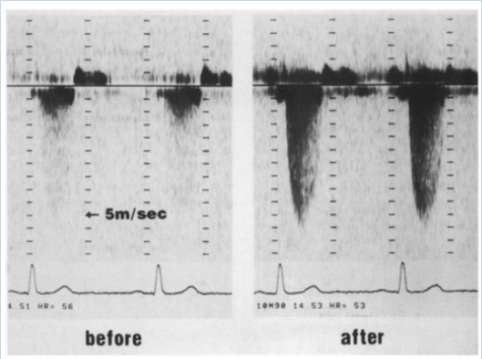
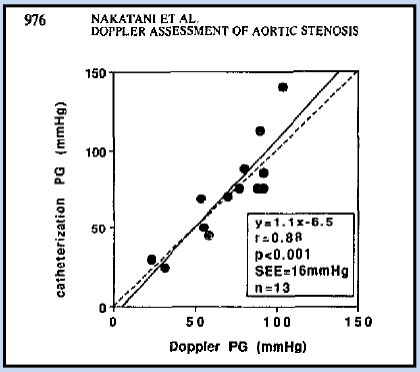
Contrast Enhancement of AS





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Clinical Evaluation of Left Heart Doppler Contrast Enhancement by a Saccharide-Based Transpulmonary Contrast Agent

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Objectives. **A multicenter study was carried out to evaluate the efficacy with which SHU 508A enhances left heart Doppler signals and improves the clinical quantification of valve disease.**

Background. **Poor signal-to-noise ratio often limits the Doppler interrogation of left heart flows. This problem may be resolved by the enhancement of Doppler signals by an ultrasound contrast agent capable of pulmonary transmission, such as the recently developed SHU 508A.**

Methods. **Left heart contrast enhancement was tested for 1) continuous wave Doppler evaluation in 51 patients with aortic stenosis, 2) pulsed Doppler transthoracic evaluation of pulmonary venous flow in 85 patients, and 3) color Doppler evaluation of mitral regurgitation in 60 patients. Studies were performed immediately before and during the intravenous administration of SHU 508A (16 ml of 200 mg/ml) and compared with unenhanced transesophageal data in representative subsets of patients.**

Results. **SHU 508A had no serious adverse effects. A significant increase in left heart Doppler signal intensity lasted for 30 to 300 s. The continuous wave Doppler velocity envelope was enhanced for all jets, but Doppler peak velocity was not altered in high quality baseline studies. However, Doppler contrast enhancement resulted in higher measured peak gradients ($p < 0.001$) in 29 patients with aortic stenosis who had poor quality baseline studies. This improved the overall correlation with invasive pressure measurements ($r = 0.73$ vs. $r = 0.89$, $p < 0.01$). The enhanced pulsed Doppler traces of transthoracic pulmonary venous flow allowed quantitative analysis in 92% patients (vs. 27% at baseline) and correlated well with peak velocities and velocity profiles obtained by transesophageal echocardiography ($r = 0.91$, $p < 0.001$). The enhanced color Doppler display of regurgitant jets increased jet area with a high interindividual variability (mean 276%), resulting in almost identical jet areas as unenhanced transesophageal values ($r = 0.97$, $p < 0.001$).**

Conclusions. **SHU 508A is a safe transpulmonary contrast agent that significantly enhances both spectral and color Doppler signals in the left heart. In specific patient subsets, the increase in signal-to-noise ratio improved the quantitative assessment of aortic stenosis, pulmonary venous flow and mitral regurgitation.**
(J Am Coll Cardiol 1995;25:500–8)

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Contrast and AS Gradient

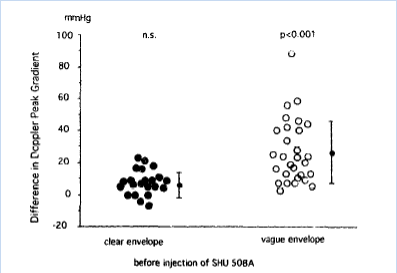

Figure 2. Apparent difference in peak Doppler gradients between recordings before and after intravenous injection of SHU 508A (Peak gradient$_{SHU\ 508A}$ − Peak gradient$_{baseline}$). Recordings were differentiated with regard to baseline quality as clear envelope (score 3 and 4) or vague envelope (score 0 to 2). Significant increase in peak gradient was observed in the vague envelope subgroup only.

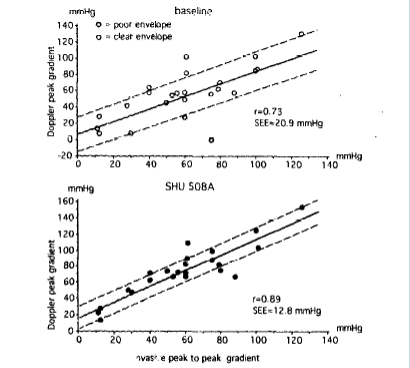

Figure 3. Correlation between invasive peak gradient **(horizontal)** and Doppler peak gradient **(vertical)** at baseline study was moderate **(top panel)** and improved with contrast enhancement **(bottom panel)**. **Dotted lines** = SEE.

von Bibra et al; JACC, 1995

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