Myocardial Contrast Echo

Anthony DeMaria

Myocardial Contrast Echocardiography: Problems and Potential

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Virtually All Ultrasound Instrument and Contrast Companies

CONTRAST ECHO

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

Contrast for LV Opacification

LV Opacification Echo Other Than Border Definition

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

Proverb

'It is dangerous to have great potential for too long a time.'

Applications of MCE in CAD

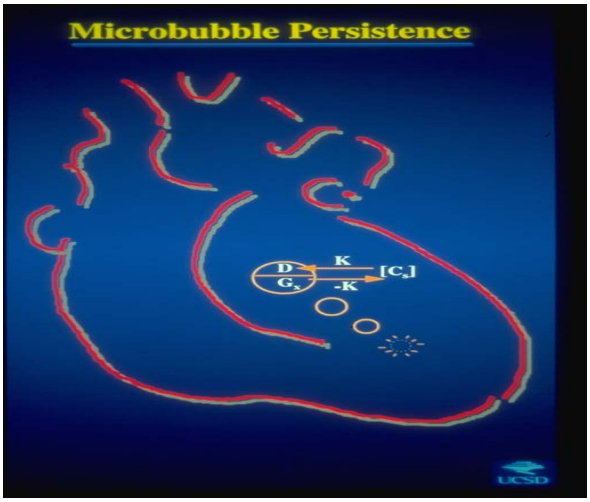
- Risk area or infarct size with MI
- Reperfusion efficacy
- No-reflow phenomenon
- Myocardial viability
- Coronary collateral flow
- Coronary artery stenosis
- Coronary flow reserve
- Targeted marker or drug delivery

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

Why?

Ultrasound contrast agents have been very difficult to successfully develop and market

Microbubble Properties: ***Shell and Gas***



Contrast Agent Properties

Agent	Mean Size (u)	Gas	Shell
Levovist	2-3	Air	(Galactose)
Optison	4.7	Perflouropropane	albumin
Definity	1.5	Perflouropropane	phospholipid
Imagent	5.0	Perflourohexane-N	Surfactant
Lumason (Sonovue)	2.5	Sulfur hexaflouride	Phospholipid
Cardiosphere	*4.0*	*Nitrogen*	*Polymer*
Acusphere	*2.0*	*Perflourocarbon*	*Polymer*

Contrast Recording Techniques

- **Destructive** *high energy*, unipulse
  - Most sensitive
  - Triggered, no motion
  - Can get tissue signals
- Power Doppler
- Ultraharmonics

- **Non-destructive** *low energy*,multipulse
  - Real-time, motion
  - Ease of use
  - Less sensitivity
- Non-linearity methods
  - Pulse inversion
  - Power modulation
  - Coherent imaging

Contrast Echo is not Contrast

- White blood volume signal superimposed upon white tissue
- Techniques needed to differentiate microbubbles from tissue
  - ECG gating
  - Harmonics
  - Non-linear signals
  - Bubble destruction (refill imaging)

Bubbles Produce Harmonic Signals

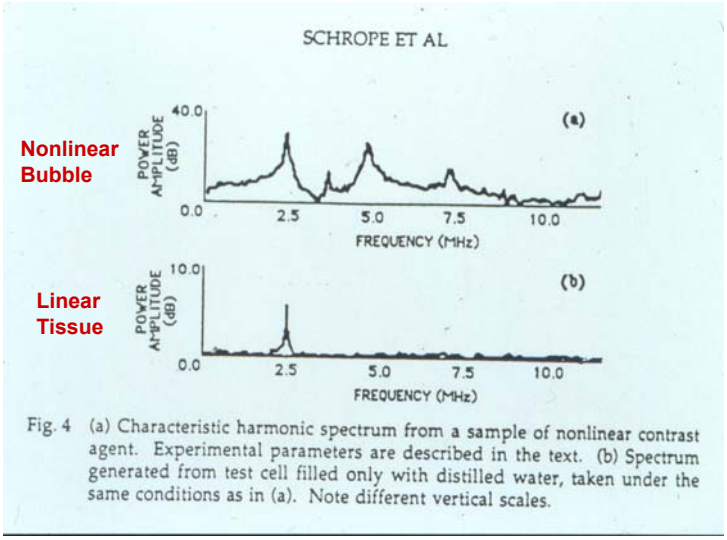
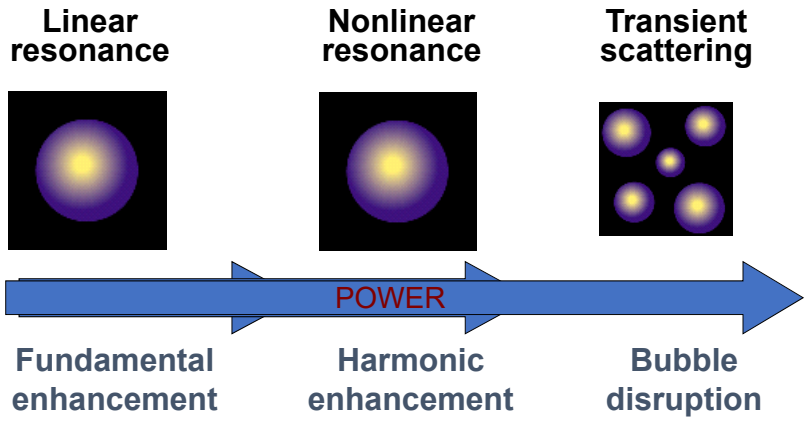
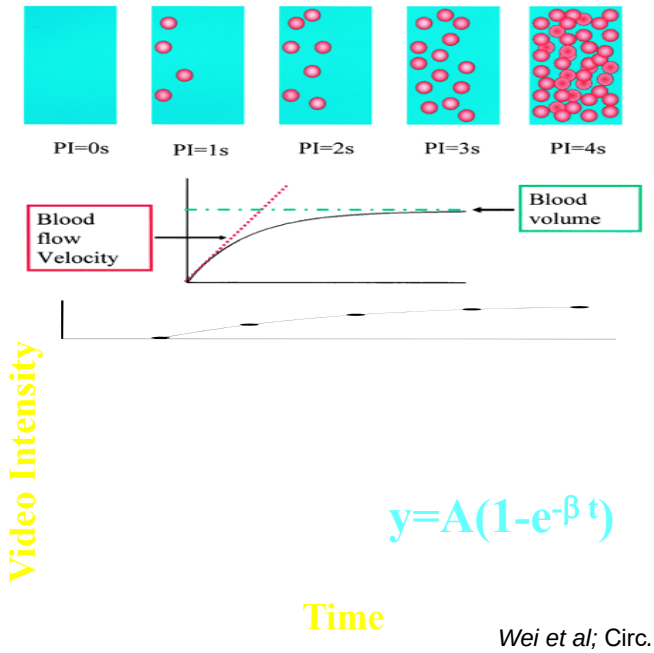


Fig. 4 (a) Characteristic harmonic spectrum from a sample of nonlinear contrast agent. Experimental parameters are described in the text. (b) Spectrum generated from test cell filled only with distilled water, taken under the same conditions as in (a). Note different vertical scales.

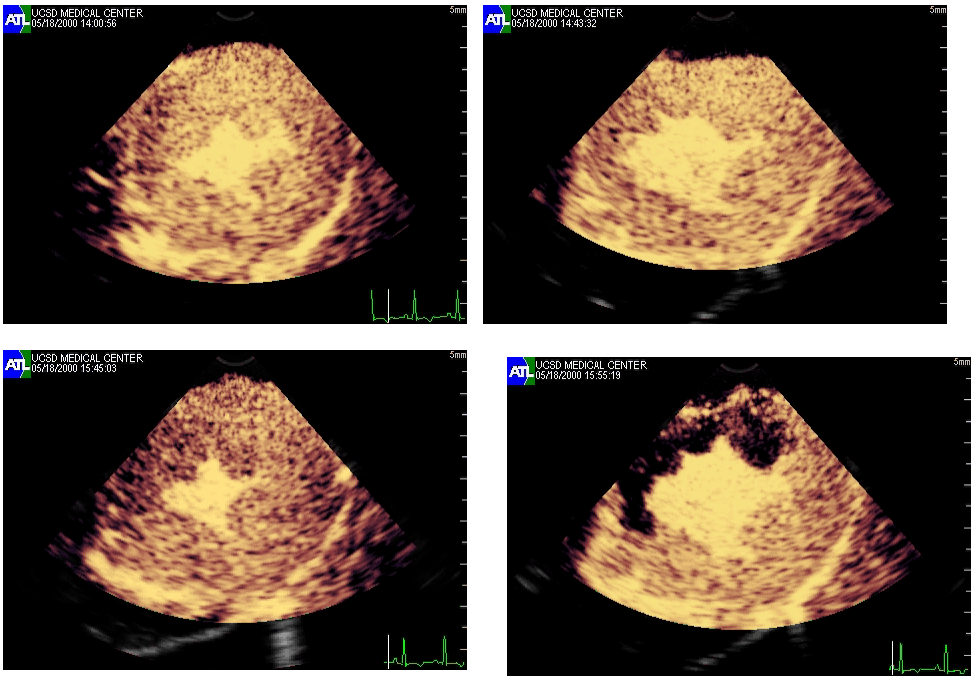
Interaction of Ultrasound and Microbubbles



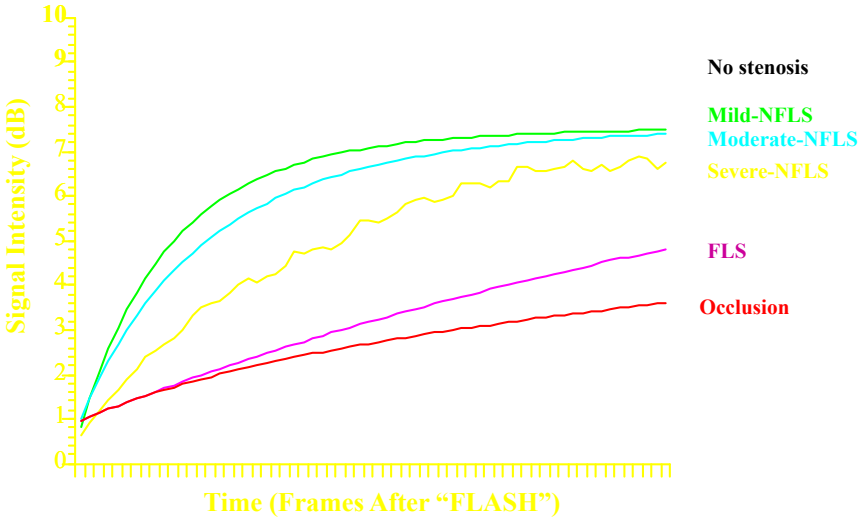


Wei et al; Circ. 97:1998

Contrast perfusion defects are time dependent

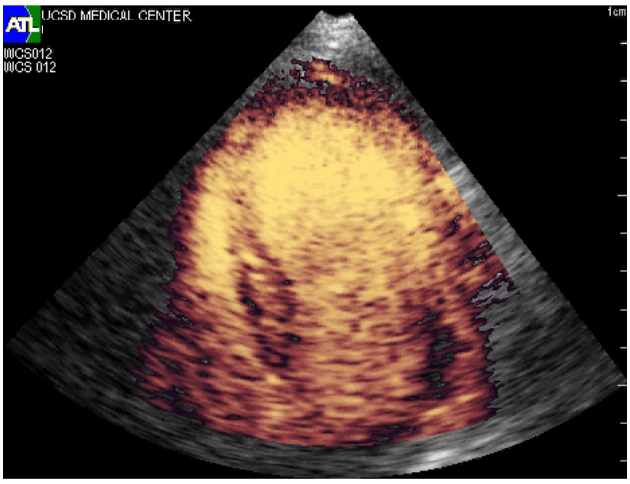


Averaged Values of Myocardial Signal Intensity

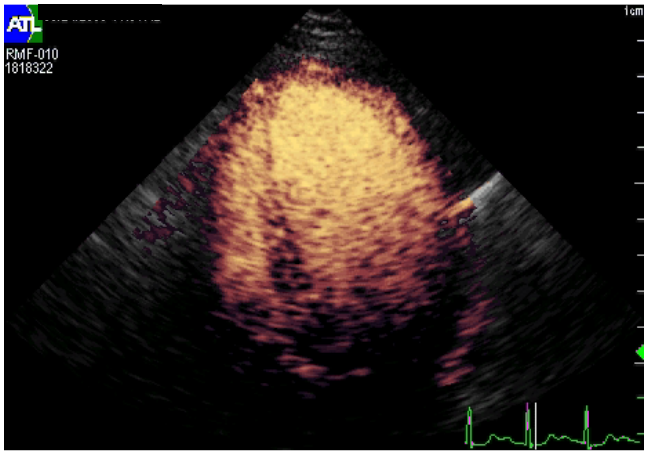


Masugata et al. Circ: 2002

Baseline



Refilling Sequence All Frames Adenosine



Detection of Myocardial Ischemia/Coronary Stenosis by MCE

Study	Year	Pts	MCE Mode	Stress Method	Criterion Standard	Sensitivity	Specificity	Concordance	Kappa
Kaul	1997	30	High MI	dipyridamole	SPECT	-	-	86%	0.71
Porter	1997	28	High MI	dipyridamole	SPECT	92%	84%	84%	-
Heinle	2000	123	High MI	adenosine	SPECT	-	-	81%	0.60
Cwajg	2000	45	Low MI	exercise/dipyridamole	Angiography	-	-	80%	0.61
Shimoni	2001	100	low MI	exercise	SPECT	-	-	76%	0.50
Shimoni	2001	44	low MI	exercise	Angiography	75%	100%	-	0.67
Porter	2001	117	low MI	dobutamine	dobutamine stress echocardiogram	-	-	91%	0.70
Porter	2001	40	low MI	dobutamine	Angiography	-	-	83%	0.65
Oraby	2001	27	high MI	dobutamine	SPECT	-	-	82%	0.49
Haluska	2001	49	high MI	doutamine	SPECT	83%	55%	-	-
Wei	2003	43	high MI	doutamine	SPECT	96%	63%	84%	0.63

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

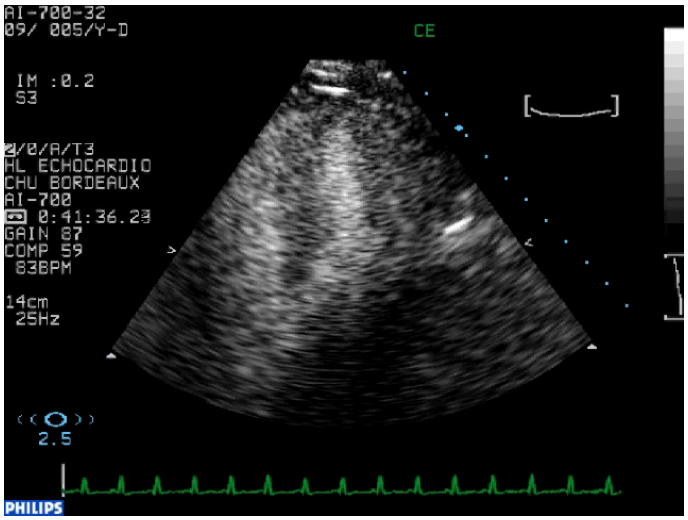
Roxy Senior[1]*, Mark Monaghan[2], Michael L. Main[3], Jose L. Zamorano[4], Klaus Tiemann[5], Luciano Agati[6], Neil J. Weissman[7], Allan L. Klein[8], Thomas H. Marwick[9], Masood Ahmad[10], Anthony N. DeMaria[11], Miguel Zabalgoitia[12], Harald Becher[13], Sanjiv Kaul[14], James E. Udelson[15], Frans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

RAMP 1 and 2

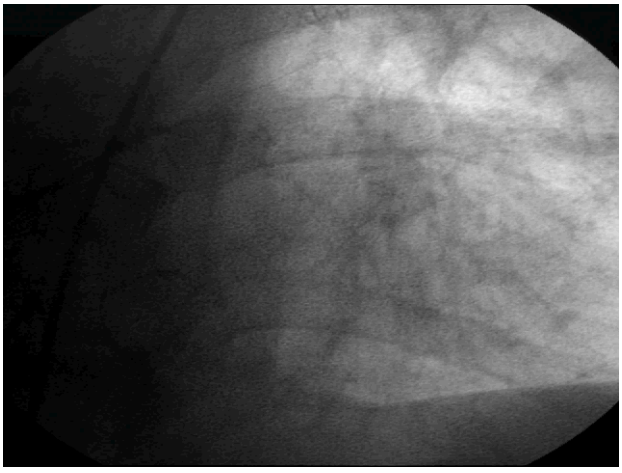
Real time assessment of myocardial perfusion

- Imagify is perflubutane polymer microspheres (poly-D,L-lactide-co glycolide and phospholipid)
- Used both real-time and gated ultraharmonic imaging
- Core laboratories for all images
  - 3 echo and 1 nuclear reader compared
- Stenosis as 70% and global jeopardy score
- 652 pts enrolled; approximately 53% CAD
- Non-inferiority design

AI 700 Dipyridamole



AI 700 Dipyridamole



RAMP 1 and 2

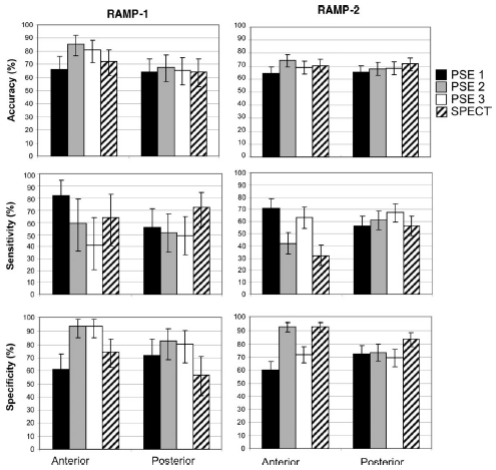
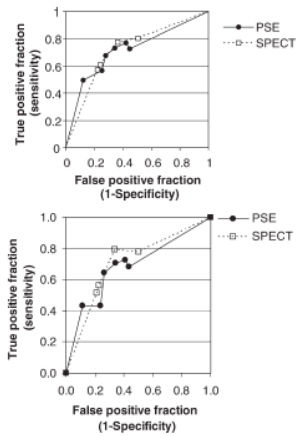
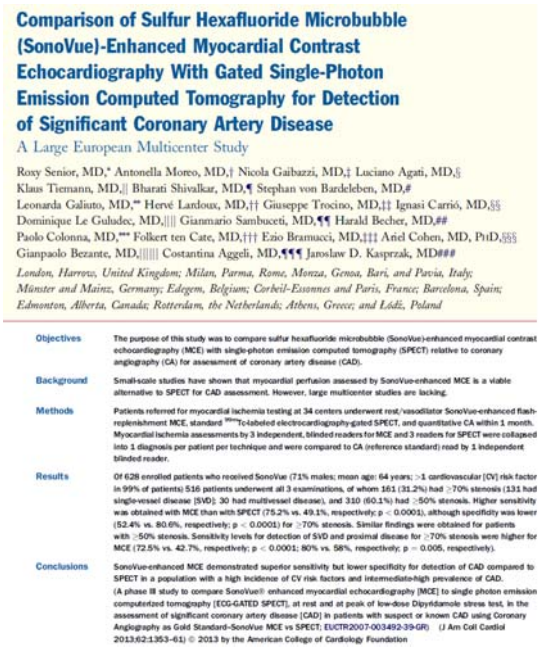


Figure 4 Defect detection and localization by vascular territory. Accuracy, sensitivity, and specificity among PSE and SPECT readers in the detection of coronary artery disease in anterior (LAD) and posterior (RCA and LCx) circulation.

ROC Analysis: RAMP 1 and 2



Senior et al: Eur J Echo; 2009



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).

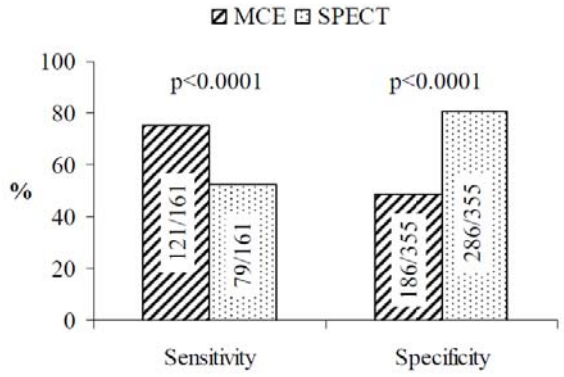
Conclusions SonoVue-enhanced MCE demonstrated superior sensitivity but lower specificity for detection of CAD compared to SPECT in a population with a high incidence of CV risk factors and intermediate-high prevalence of CAD.

(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)

MCE vs Spect

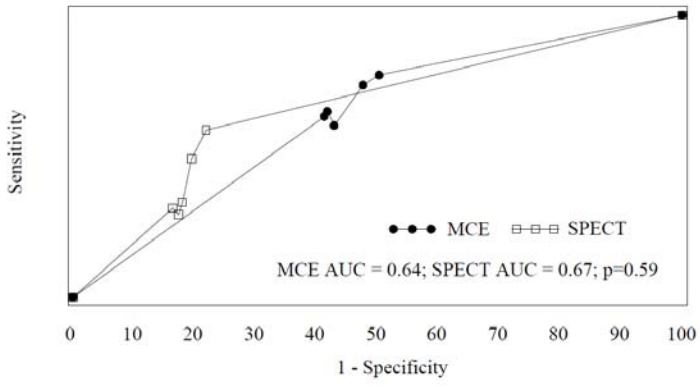
- 513 pts with known or suspected CAD
- Sulphur hexaflouride continuous infusion
- Dipyridamole stress with destroy/refill
- SPECT and cor angio in standard fashion
- 3 expert readers for each: collapsed into 1
- MCE + if no stress refill by after 4 cycles
- SPECT by visual assessment
- Non-inferiority design

Diagnostic Accuracy: MCE vs SPECT



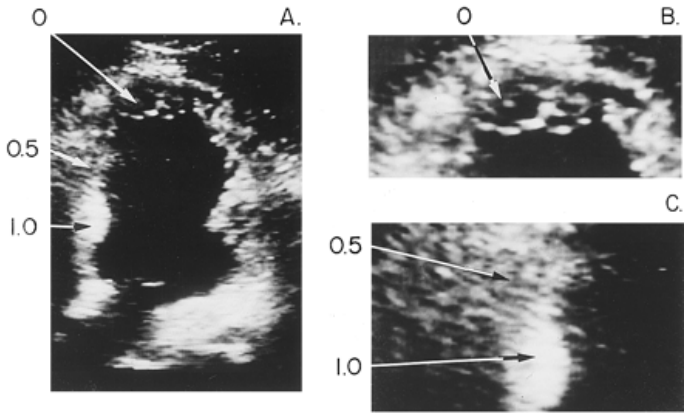
Senior et al; JACC, 2013

ROC Analysis: MCE vs SPECT



Senior et al; JACC, 2013

Viability by MCE



Ragosta et al; , 89:1994

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)**

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