SOSPETTO CLINICO DI CORONAROPATIA:

L'INNEGABILE VALORE DELLO STRESS-ECO, RUOLO PRESENTE E FUTURO

Nicola Gaibazzi

Parma

La Diagnosi di CAD

European Heart Journal (2013) **34**, 2949–3003
doi:10.1093/eurheartj/eht296

ESC GUIDELINES

2013 ESC guidelines on the management of stable coronary artery disease

The Task Force on the management of stable coronary artery disease of the European Society of Cardiology

Table 12 Characteristics of tests commonly used to diagnose the presence of coronary artery disease

	Diagnosis of CAD	
	Sensitivity (%)	Specificity (%)
Exercise ECG [a, 91, 94, 95]	45–50	85–90
Exercise stress echocardiography[96]	80–85	80–88
Exercise stress SPECT[96-99]	73–92	63–87
Dobutamine stress echocardiography[96]	79–83	82–86
Dobutamine stress MRI[b,100]	79–88	81–91
Vasodilator stress echocardiography[96]	72–79	92–95
Vasodilator stress SPECT[96, 99]	90–91	75–84
Vasodilator stress MRI[b,98, 100-102]	67–94	61–85
Coronary CTA[c,103-105]	95–99	64–83
Vasodilator stress PET[97, 99, 106]	81–97	74–91

Table 13 Clinical pre-test probabilities[a] in patients with stable chest pain symptoms[108]

	Typical angina		Atypical angina		Non-anginal pain	
Age	Men	Women	Men	Women	Men	Women
30–39	59	28	29	10	18	5
40–49	69	37	38	14	25	8
50–59	77	47	49	20	34	12
60–69	84	58	59	28	44	17
70–79	89	68	69	37	54	24
>80	93	76	78	47	65	32

ECG = electrocardiogram; PTP = pre-test probability; SCAD = stable coronary artery disease.
[a] Probabilities of obstructive coronary disease shown reflect the estimates for patients aged 35, 45, 55, 65, 75 and 85 years.
• Groups in white boxes have a PTP <15% and hence can be managed without further testing.

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The declining frequency of inducible myocardial ischemia during stress echocardiography over 27 consecutive years (1983–2009)☆

Clara Carpeggiani MD *, Patrizia Landi BSc, Claudio Michelassi BSc, Rosa Sicari MD, PhD, Eugenio Picano MD, PhD
CNR Institute of Clinical Physiology, Pisa, Italy

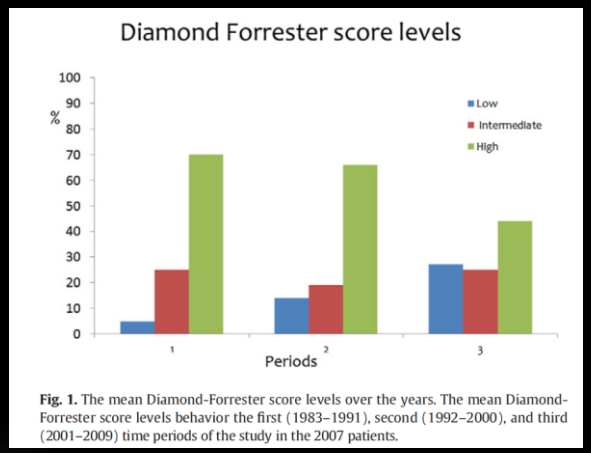


Fig. 1. The mean Diamond-Forrester score levels over the years. The mean Diamond-Forrester score levels behavior the first (1983–1991), second (1992–2000), and third (2001–2009) time periods of the study in the 2007 patients.

Il mito dei tests provocativi, stresseco compreso, che avrebbero 85% di sensibilità per CAD ostruttiva…

Oggi non è più così per almeno tre motivi:

-si inizia a rimuovere il referral bias che gonfiava la sensibilità,

-non si studiano più solo pazienti a medio-alto rischio come nei vecchi studi, e

-spesso venivano analizzati tenendo >70% di stenosi come presenza di CAD

PURTROPPO È OGGI INCONTESTABILE, DATI RECENTI ALLA MANO, CHE L'ANALISI DELLA CINETICA È DA SOLA INSUFFICIENTE, PER LA SUA BASSA SENSIBILITÀ, NELL'UTILIZZO SPECIFICO PER

DIAGNOSI DI CAD

Coronary Artery Disease

Detection of Significant Coronary Artery Disease by Noninvasive Anatomical and Functional Imaging

The EVINCI study

Neglia et al. Circ cardiovasc imaging 2015

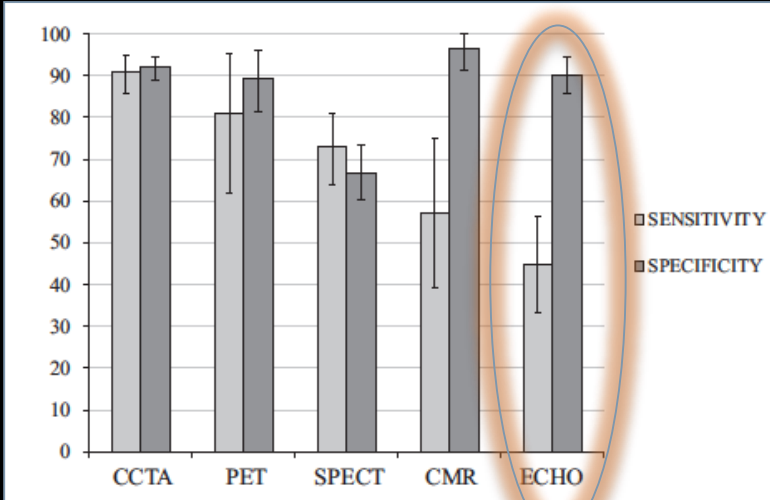


Figure 3. Sensitivity and specificity of noninvasive imaging techniques.
CCTA indicates coronary computed tomography angiography; CMR, cardiac magnetic resonance; ECHO, echocardiography; PET, positron emission tomography; and SPECT, single-photon computed emission tomography.

Cinetica (CMR+Echo)

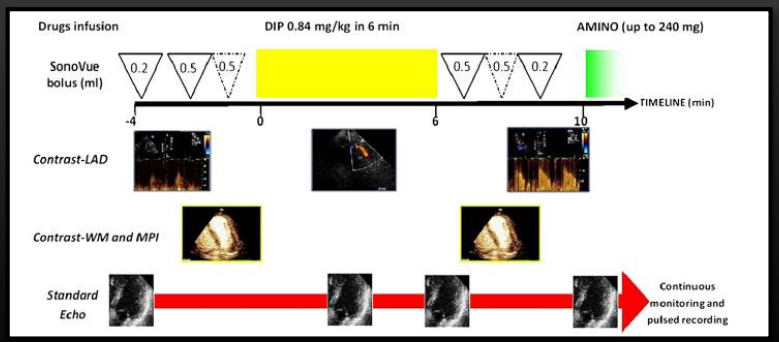
Sensibilità 49% (36% verif bias corr)
Spec 90%

Perfusione (SPECT+PET)

Sensibilità 74% (59% verif bias corr)
Spec 70%

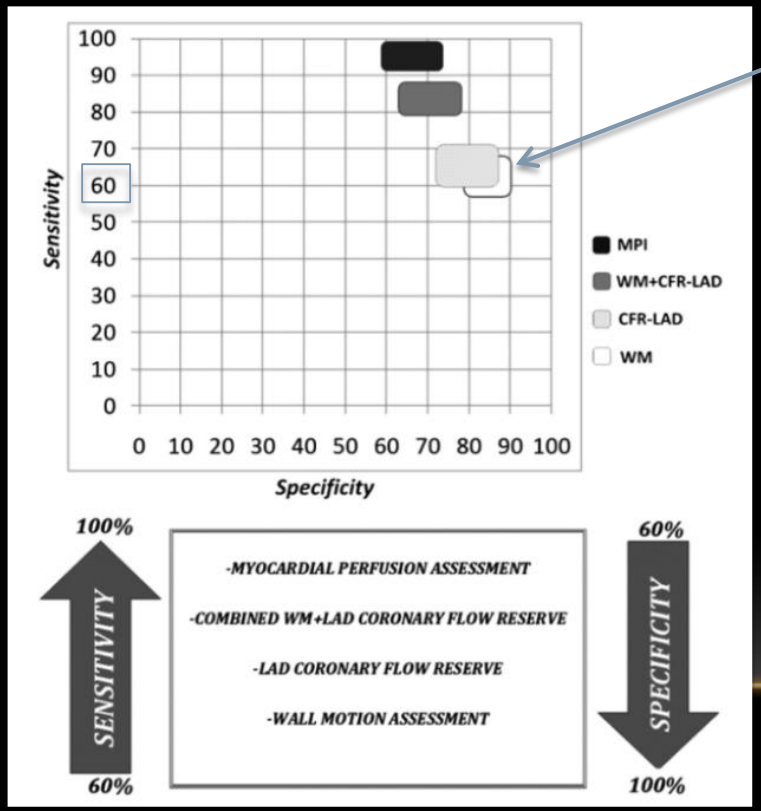
Detection of Coronary Artery Disease by Combined Assessment of Wall Motion, Myocardial Perfusion and Coronary Flow Reserve: A Multiparametric Contrast Stress-Echocardiography Study

Nicola Gaibazzi, MD, PhD, Fausto Rigo, MD, and Claudio Reverberi, MD, *Parma and Mestre-Venice, Italy*



400 pts, undergoing clinically indicated angiography

Dipyridamole 0.84mg/kg/6min



Cinetica

The addition of contrast- facilitated CFR-LAD or Perfusion imaging measurement also brings significantly higher sensitivity with small decrease in specificity

Gaibazzi N, Rigo F, Reverberi C. J Am Soc Echocardiogr. 2010;23:1242-50.

Journal of the American Heart Association
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Clinical Implications of Referral Bias in the Diagnostic Performance of Exercise Testing for Coronary Artery Disease

Joseph A. Ladapo, Saul Blecker, Michael R. Elashoff, Jerome J. Federspiel, Dorice L. Vieira, Gaurav Sharma, Mark Monane, Steven Rosenberg, Charles E. Phelps and Pamela S. Douglas

J Am Heart Assoc. 2013;2:e000505; originally published December 13, 2013;
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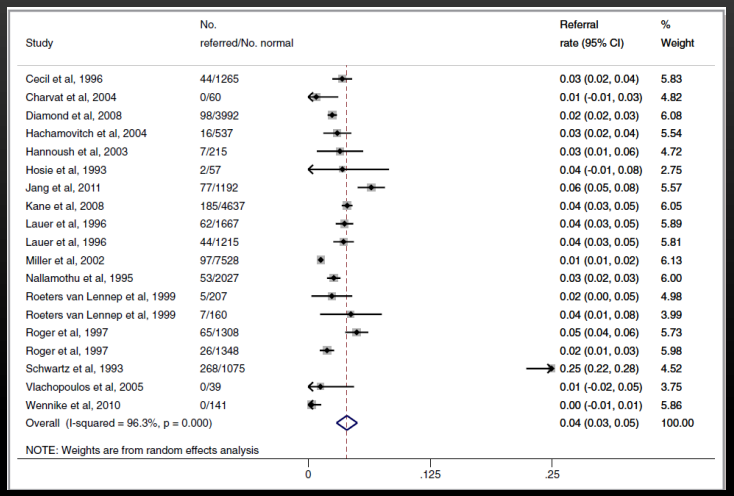

Conclusions—Exercise echocardiography and myocardial perfusion imaging are considerably less sensitive and more specific for coronary artery disease after adjustment for referral. Given these findings, future work should assess the comparative ability of these and other tests to rule-in versus rule-out coronary artery disease. (***J Am Heart Assoc*. 2013;2:e000505 doi: 10.1161/JAHA.113.000505**)

Exercise

Table 2. Diagnostic Effectiveness of Exercise ECHO and MPI With and Without Adjustment for Referral

	ECHO		MPI	
	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Sensitivity, % (95% CI)	Specificity, % (95% CI)
Unadjusted*	84 (80 to 89)	77 (69 to 86)	85 (81 to 88)	69 (61 to 78)
Adjusted†	34 (27 to 41)	99 (99 to 100)	38 (31 to 44)	99 (99 to 100)

ECHO indicates echocardiography; MPI, myocardial perfusion imaging.
*Diagnostic effectiveness based on random-effects meta-analysis of sensitivity and specificity reported in 15 studies of exercise ECHO and 30 studies of exercise MPI (45 studies in total).
†Adjusted for referral rates to cardiac catheterization after abnormal or normal exercise test result.

All provocative tests demonstrate a big problem with sensitivity and consequent false negative tests if referral bias is accounted for..
In practice we need much higher sensitivity, even if this would cost a small decrease in specificity which is instead very high

Non è colpa dello stressor (Dip vs Dob vs Exe) ma limitazione di sensibilità insita nell'essere l'ultimo step nella cascata ischemica

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Safety of Dobutamine Stress Real-Time Myocardial Contrast Echocardiography

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Omaha, Nebraska

Dobutamine

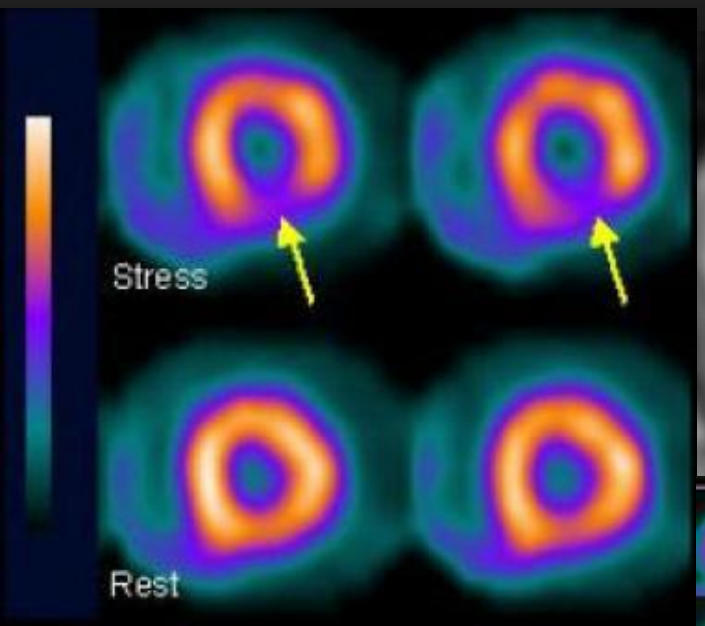
METHODS Over a four-year period, 1,486 patients underwent dobutamine stress RTCE

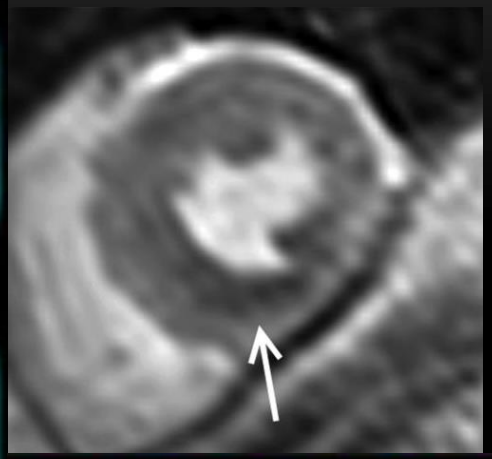
Table 4. Diagnostic Parameters of MPI and WMA by RTCE for Detecting Angiographically Significant Coronary Artery Disease

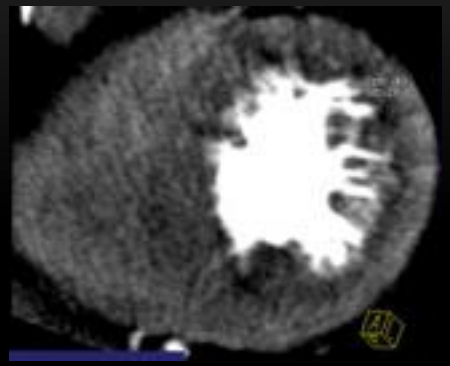
	WMA	MPI
Sensitivity	115/180; 64% (57%–71%)	173/180; 96% (93%–99%)*
Specificity	50/69; 72% (62%–83%)	35/69; 51% (39%–63%)*
Positive predictive value	115/134; 86% (80%–92%)	173/207; 84% (79%–89%)
Negative predictive value	50/115; 43% (60%–72%)	35/42; 83% (78%–88%)*
Accuracy	165/249; 66% (60%–72%)	208/249; 84% (79%–88%)*

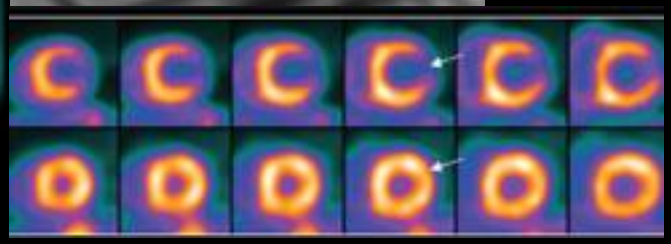
In Real-life Cohorts Stressecho Has Lower Sensitivity For Obstructive CAD>50% Than Typically Reported

But Referral Bias is still Present and Inflates These Sensitivity Numbers too..









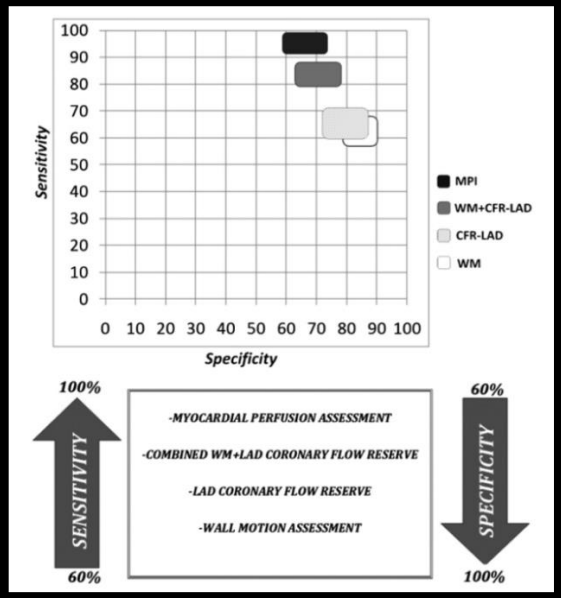
SPECT, PET, CMR, CT

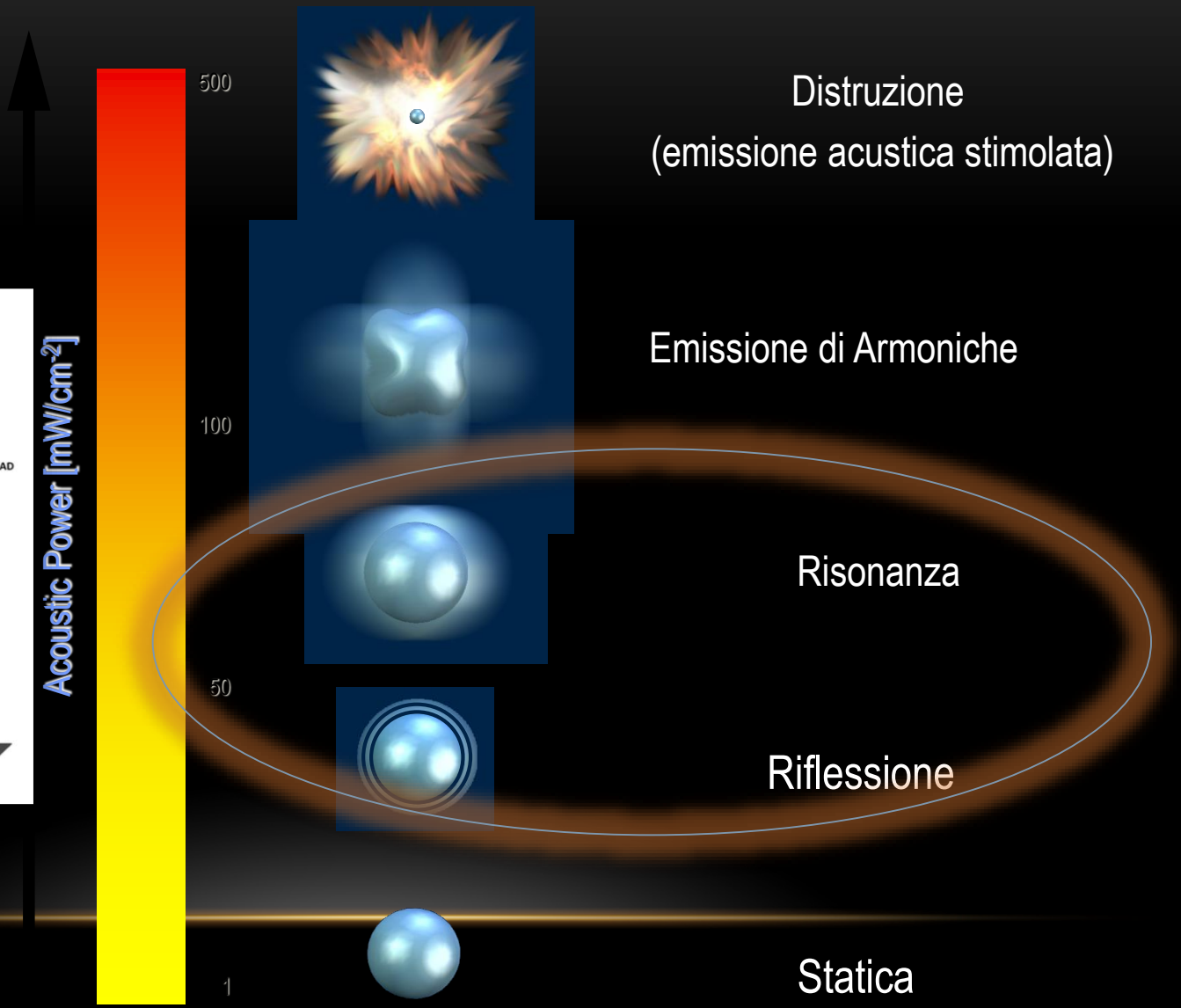
Very useful perfusion techniques but they share 2 limitations:

a) ionizing radiation

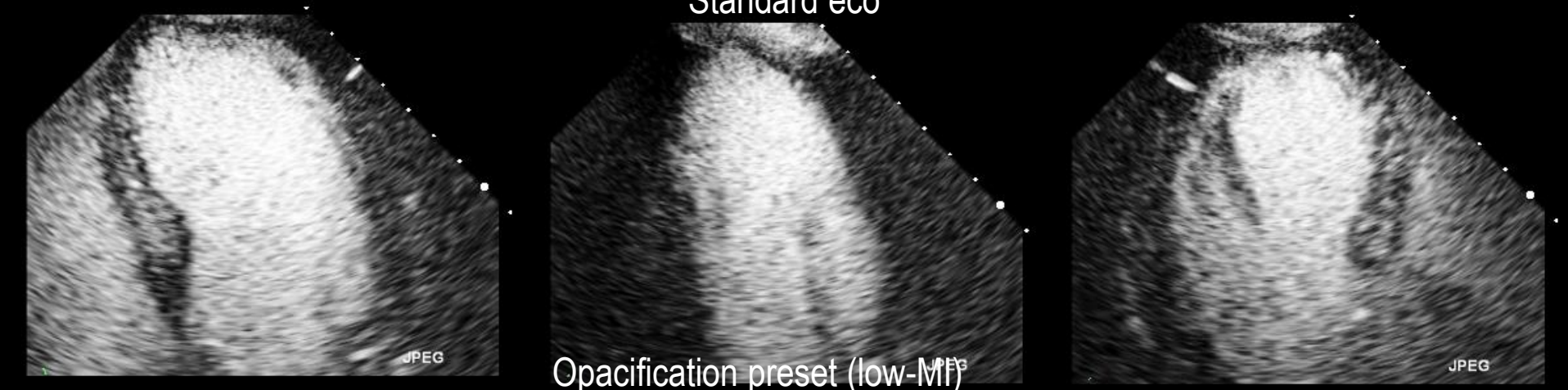
b) realtime cardiac imaging is not available during such exams

La misurazione della riserva coronarica su LAD e l'utilizzo del contrasto, soprattutto per analisi di perfusione, sono metodiche che aumentano la sensibilità diagnostica per CAD

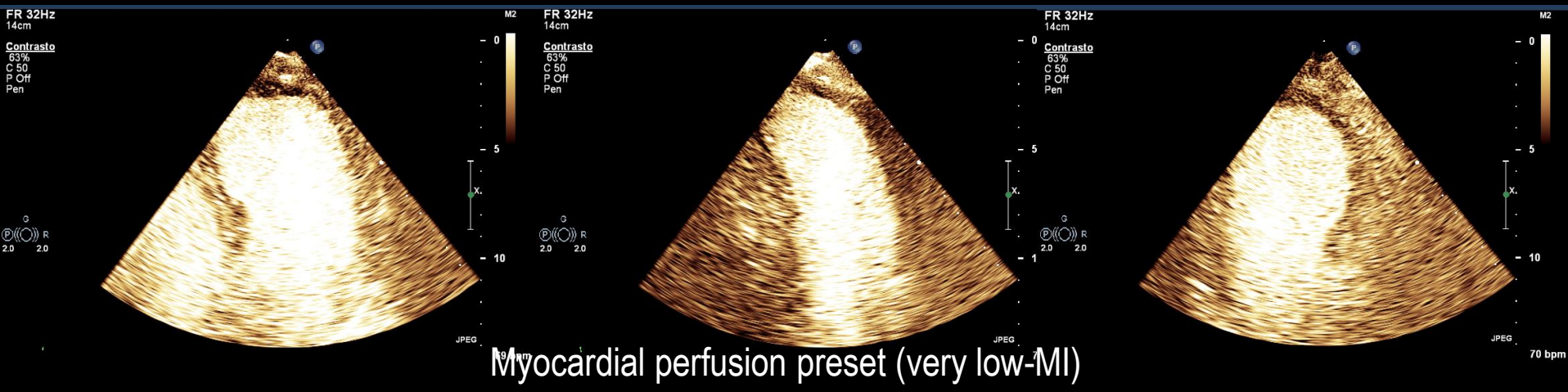




Standard eco



Opacification preset (low-MI)

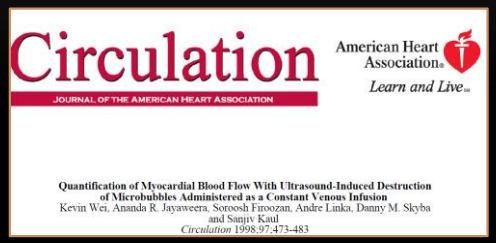


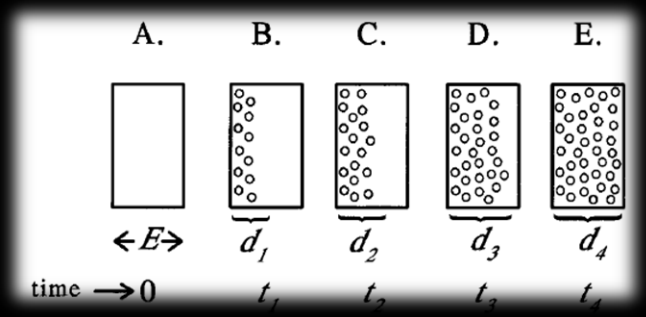
Myocardial perfusion preset (very low-MI)

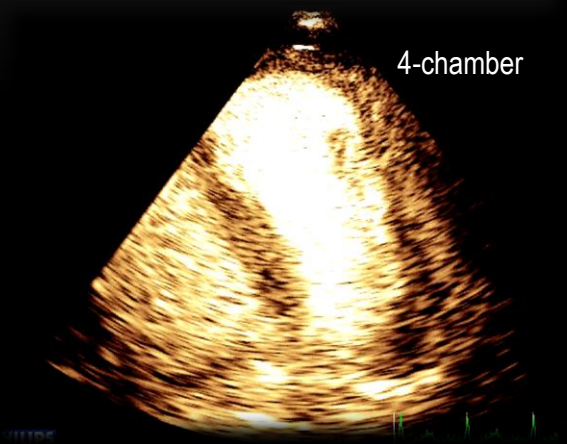
HOW DOES PERFUSION LOOK LIKE AT STRESSECHO? LET'S SEE SOME EXAMPLES..

1.5-2 seconds after flashing gets refilled if no stenosis>50% is present

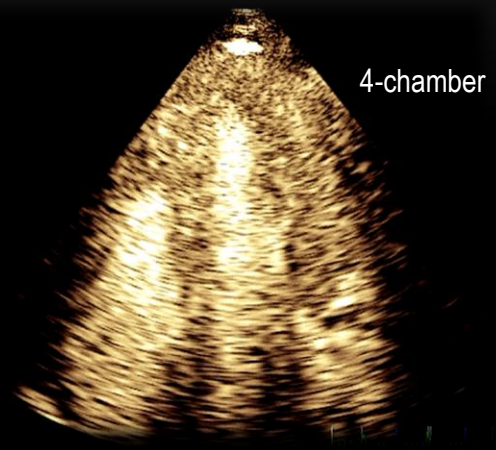
MyocardialBloodFlow = MBVolume × MBVelocity



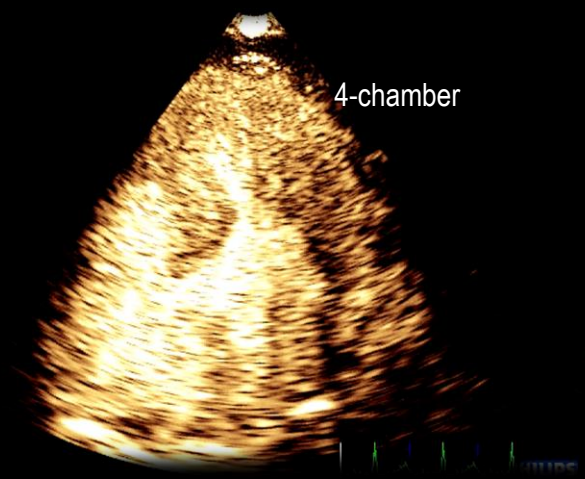




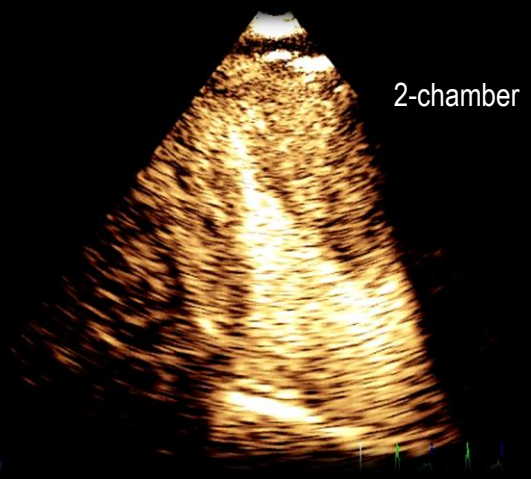
Real-time imaging:



Endsystolic triggering:
1 endsystolic image per cycle

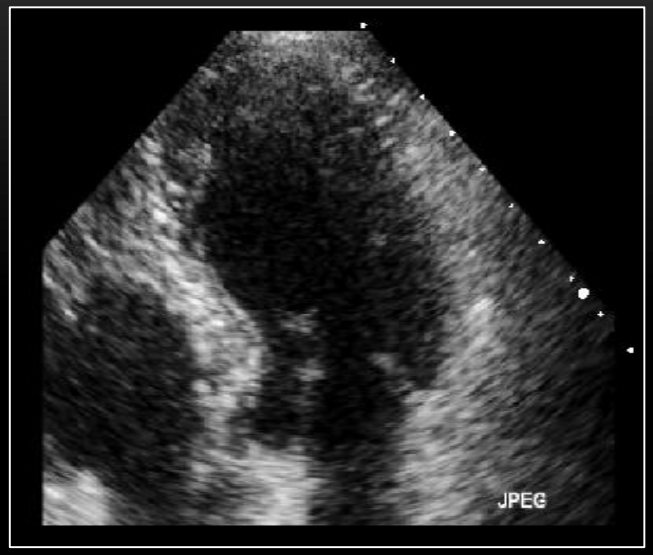


Endsystolic triggering:
1 endsystolic image per cycle

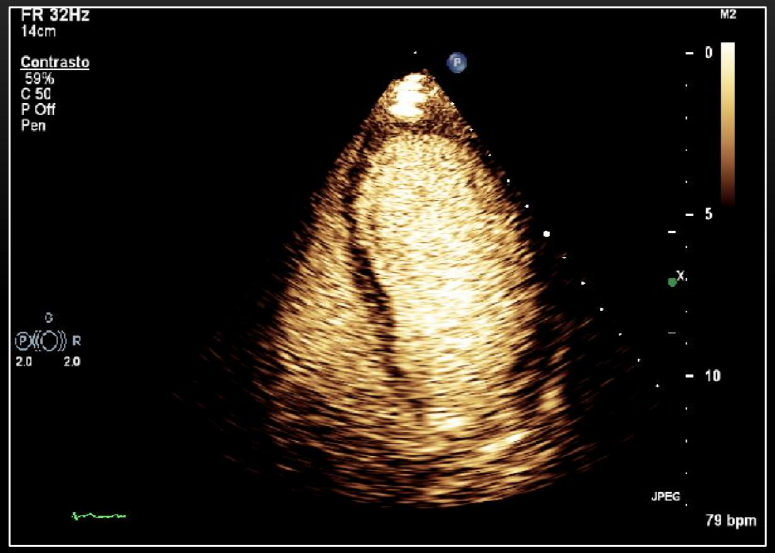


Endsystolic triggering:
1 endsystolic image per cycle

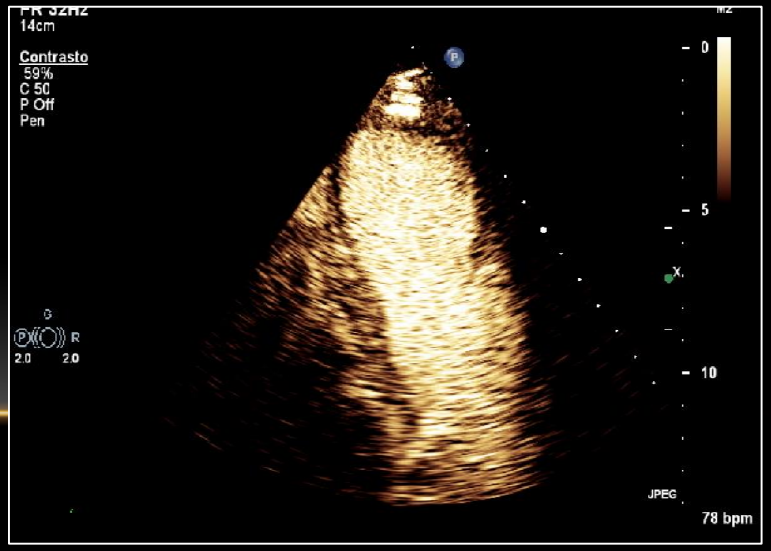
STRESSECO SENZA E CON CONTRASTO: PICCOLE MA SENSIBILI DIFFERENZE, ANCHE A RIPOSO



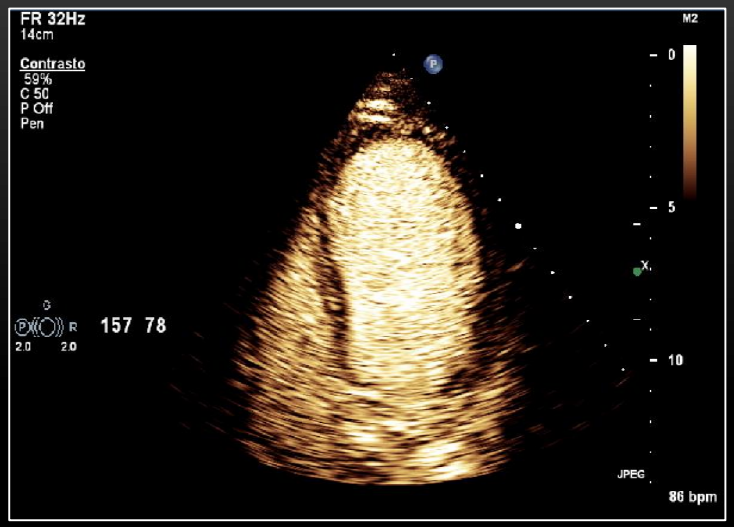
4CH



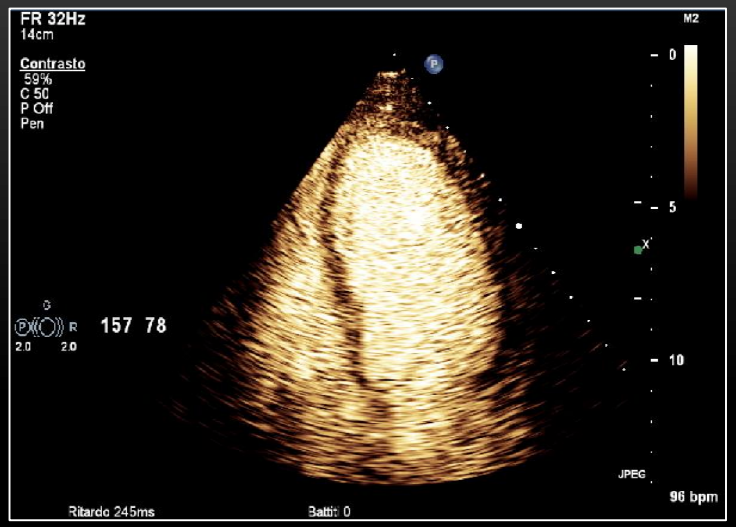
2CH

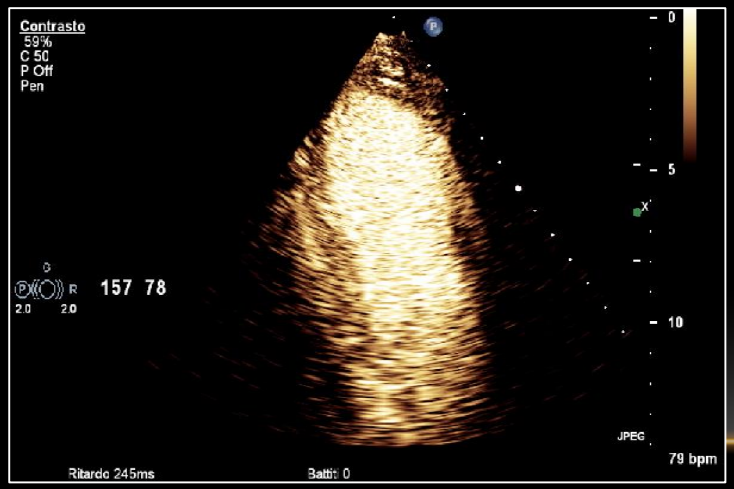


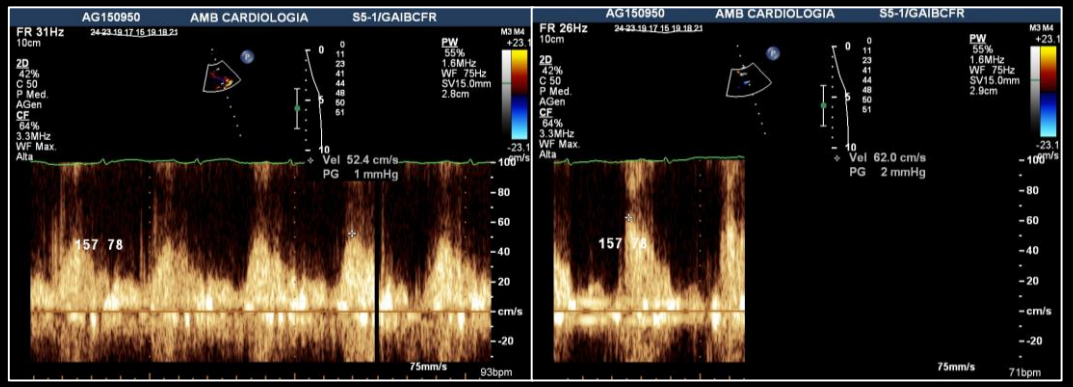
STRESS



4CH







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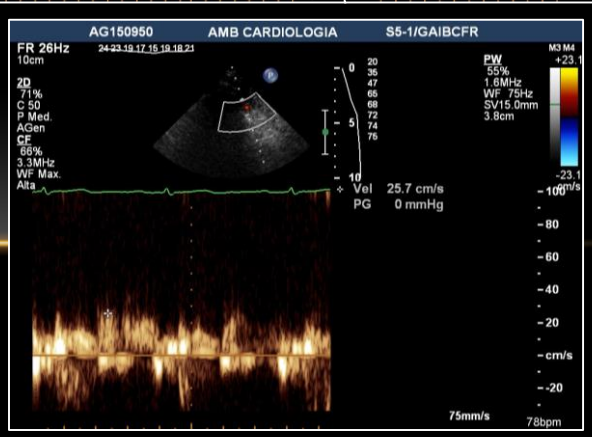
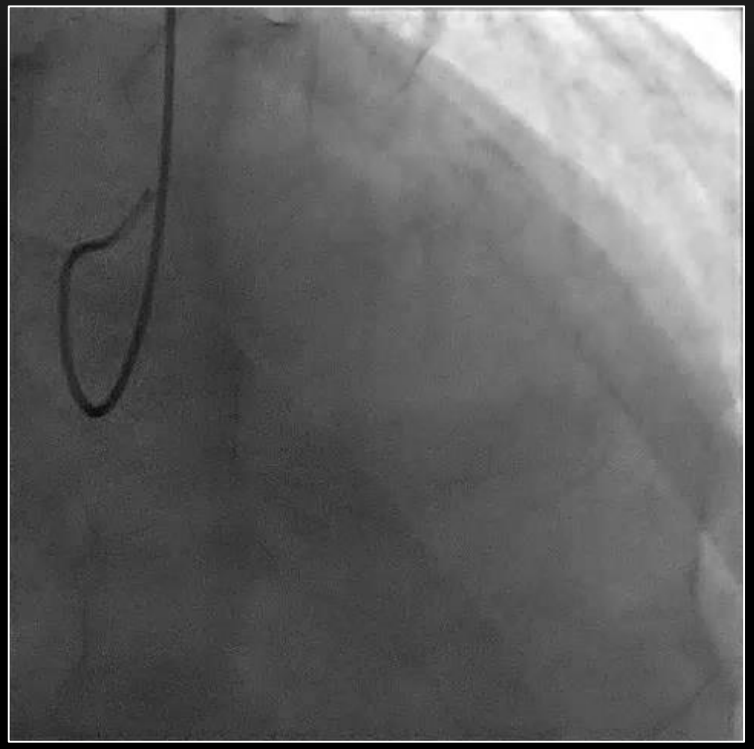


CFR-LAD=2 or >2



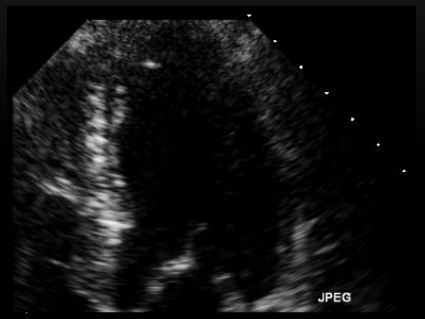
WITHOUT THE ENHANCING EFFECT OF CONTRAST (DUE TO HYPOPERFUSED SUBENDOCARDIAL REGIONS) WALL MOTION COULD APPEAR NORMAL AND CFR-LAD ALSO

CASO: PAZIENTE DI 58 ANNI CON EPISODIO DI DOLORE TORACICO A RIPOSO, NORMALE hs-TROP ED ECG

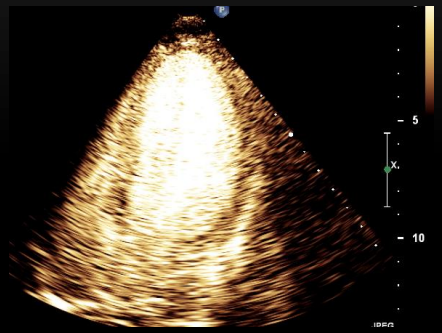
- *Maschio*
- *Iperteso, trattato con sartani*
- *Ipercolesterolemia*
- *No Diabete*
- *Non familiarità per CAD*
- *Obeso (BMI=31)*

STRESSECO MEDIANTE PROTOCOLLO STANDARD, DIPYRIDAMOLO 0.84MG/KG/6MIN CON AGGIUNTA DI CONTRASTO

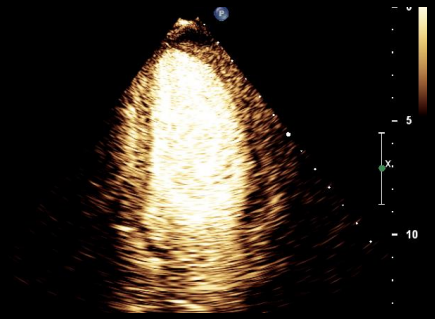
REST



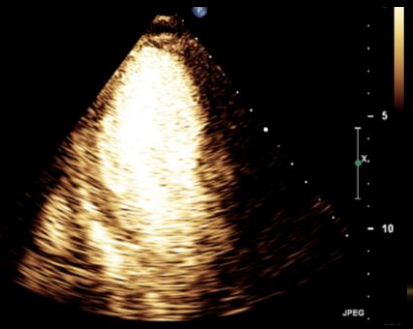
4-ch



2-ch



3-ch



REST

DOPO DIPIRIDAMOLO 0.84MG/KG/6MIN

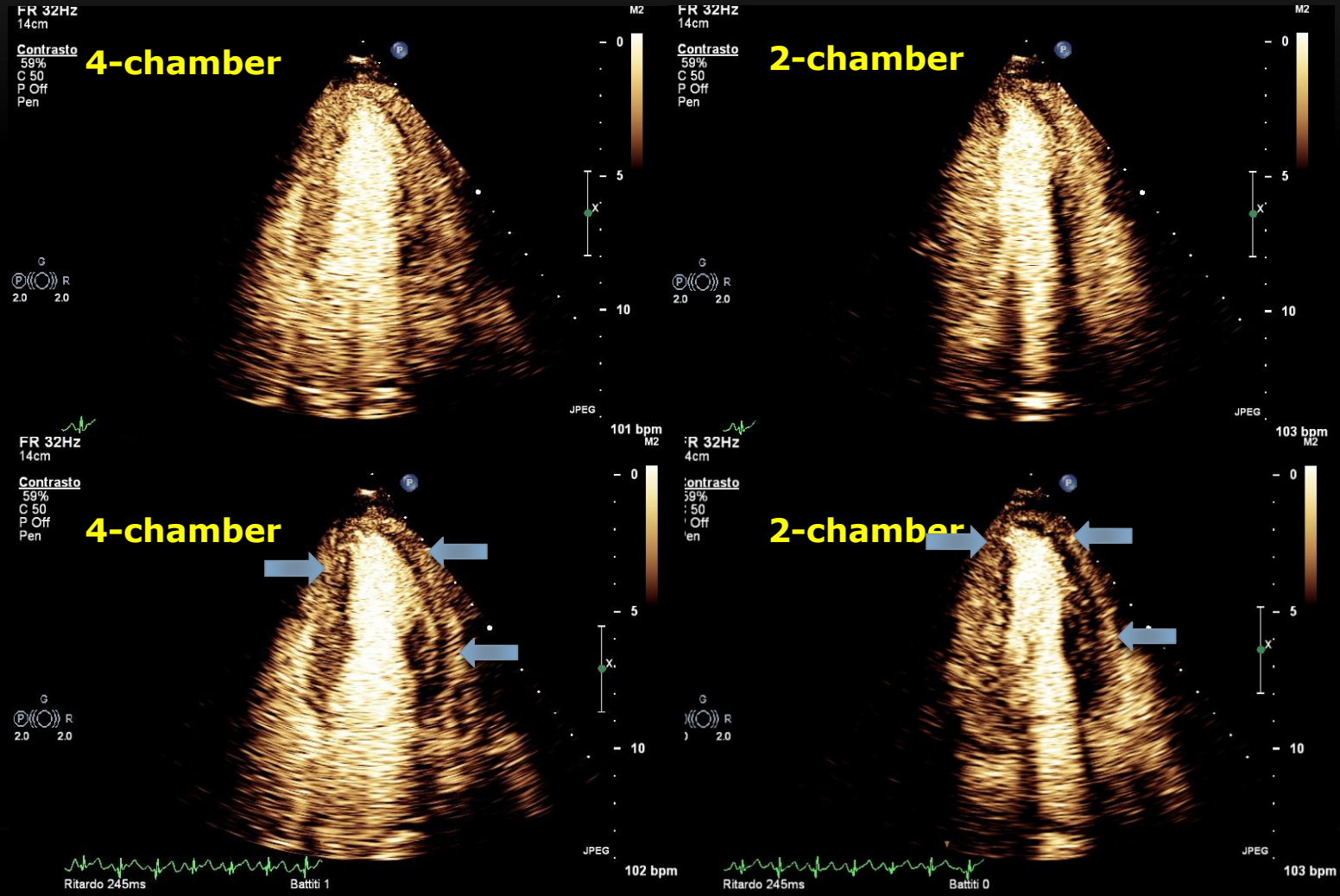
STRESS

4-ch

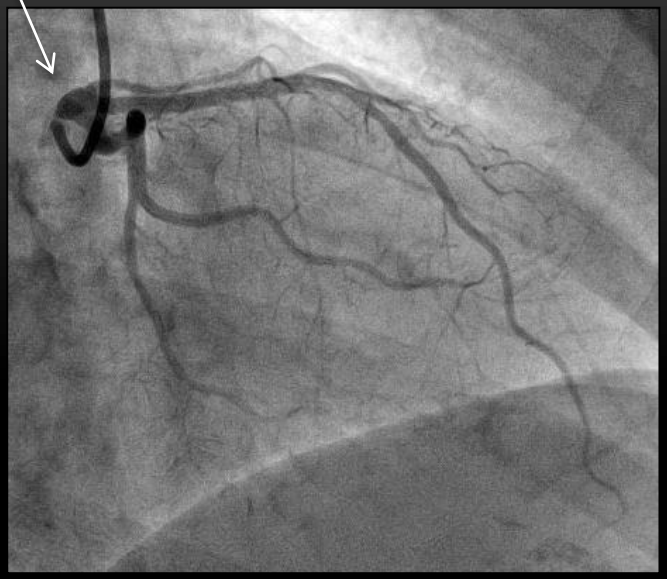
2-ch

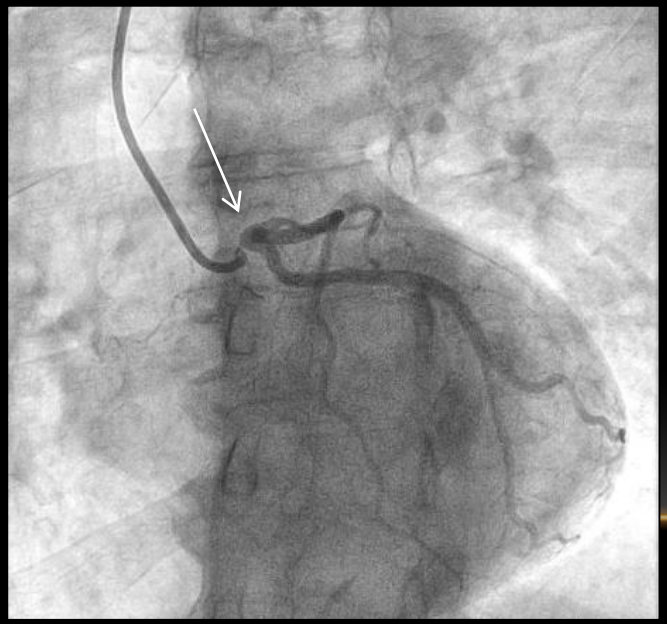
3-ch

Ora vediamo
la perfusione in fase di stress (endsystolic triggered images)



at 4 beats after flash **at 4 beats after flash**





OSTIAL LEFT MAIN TRUNK DISEASE

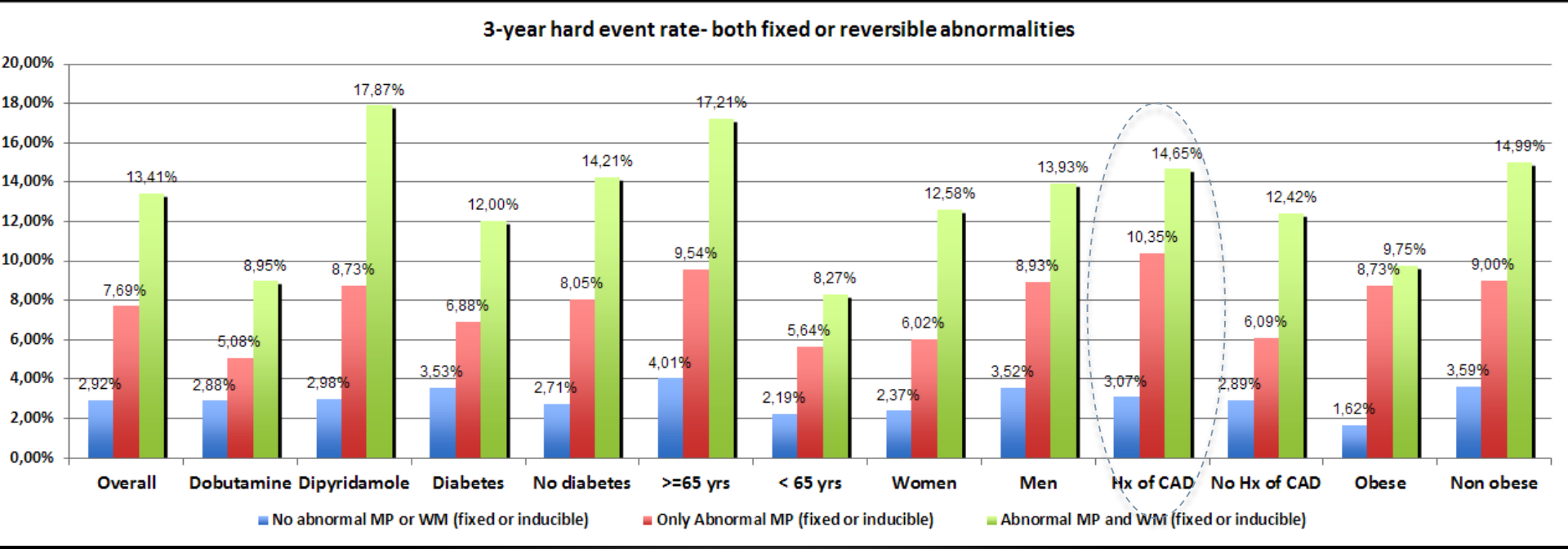
Il tipico caso che dimostra come lo stressecho non funzioni bene se si analizza solo la wall motion

Si pensa che l'aumento di sensibilità diagnostica serva solo a rilevare malattia intermedia monovasale e non quella prognosticamente più severa, ma invece in molte situazioni come i bi o trivasali la cinetica può fallire

La Prognosi della CAD stabile

ASSESSING MYOCARDIAL PERFUSION WITH REAL TIME STRESS CONTRAST ECHOCARDIOGRAPHY TO RECLASSIFY RISK WITHIN THE GENERAL POPULATION AND KEY PATIENT SUBGROUPS

Thomas Porter, Reverberi C , Juefei Wu, Feng Xie, Valentina Lorenzoni, Sabrina Molinaro, Nicola Gaibazzi



>3200 patients, presented AHA 2014

Combining Stress Wall Motion + Myocardial Perfusion Gives An Incremental Prognostic Value Over Standalone Wall

Prognostic Value of Dobutamine Stress Myocardial Contrast Perfusion Echocardiography

Jeane M. Tsutsui, MD; Abdou Elhendy, MD, PhD; James R. Anderson, PhD; Feng Xie, MD; Anna C. McGrain, RN, BSN; Thomas R. Porter, MD

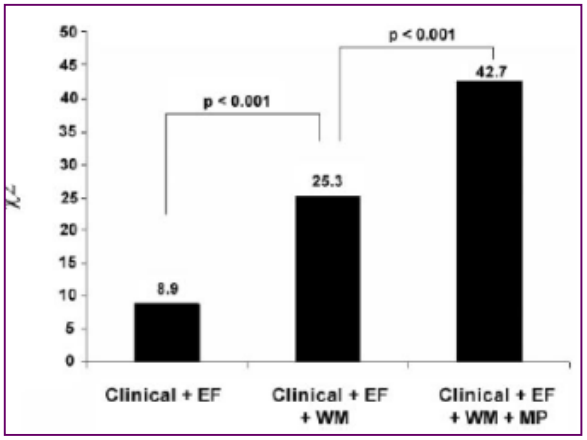
Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION

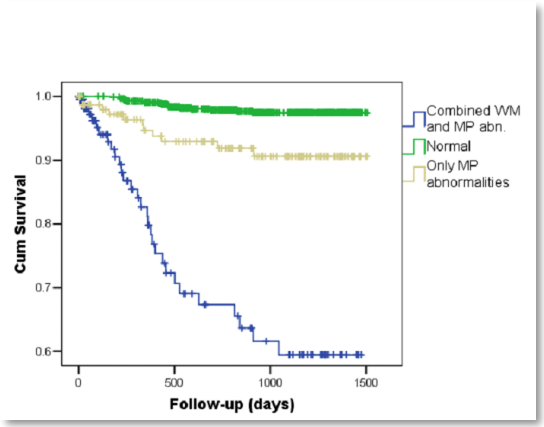
American Heart Association.

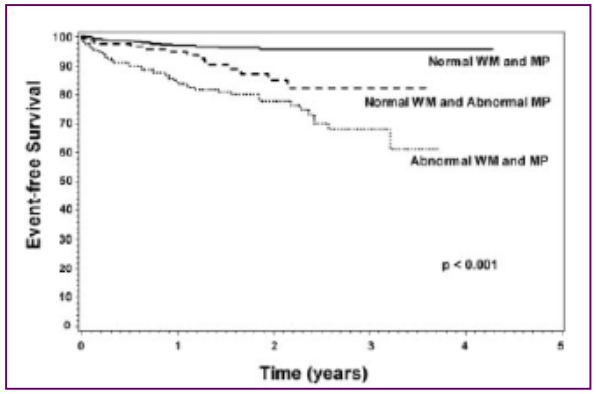
Prognostic Value of High-Dose Dipyridamole Stress Myocardial Contrast Perfusion Echocardiography

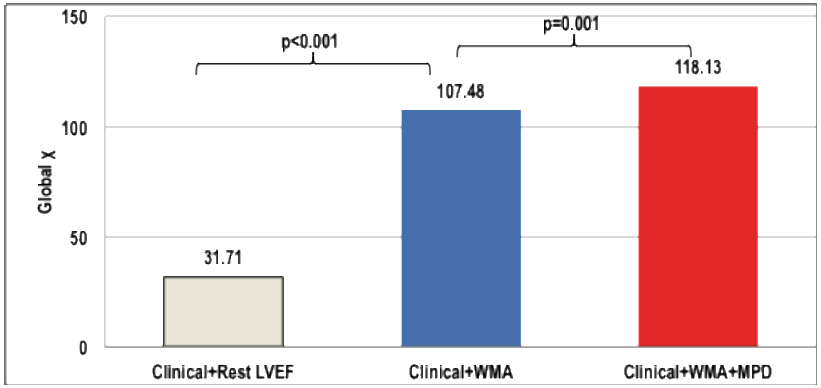
Nicola Gaibazzi, Claudio Reverberi, Valentina Lorenzoni, Sabrina Molinaro and Thomas R. Porter



STRESS AND REST PERFUSION INCREMENTAL ON TOP OF WM







Tsutsui JM, Porter TR. et al Prognostic value of dobutamine stress myocardial contrast perfusion echocardiography. Circulation. 2005 Sep 6;112:1444-50.

Gaibazzi N, Reverberi C, Lorenzoni V, Molinaro S, Porter TR –Circulation 2012

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EUROPEAN SOCIETY OF CARDIOLOGY®

European Heart Journal
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ESC/EACTS GUIDELINES

2014 ESC/EACTS Guidelines on myocardial revascularization: web addenda

The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)

Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI)

Le linee guida sulla rivascolarizzazione si scontrano con la paucità di dati circa la guida dei tests di ischemia nell'indicazione alla rivascolarizzazione, sul cui valore prognostico in questo setting rimangono molti dubbi L'ISCHEMIA TRIAL aiuterà speriamo a dirimere le nebbie conoscitive

6. Revascularization for stable coronary artery disease

6.1 Rationale for revascularization

6.1.1 Impact on symptoms, quality of life, and anti-angina drugs

Angina is associated with impaired quality of life, reduced physical endurance, mental depression, and recurrent hospitalizations and office visits.[46] Revascularization by PCI or CABG more effectively relieves angina, reduces the use of anti-angina drugs, and improves exercise capacity and quality of life than with a strategy of medical therapy alone (*Table 2*).[47–53]

The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) study showed an incremental benefit from PCI over medical therapy in terms of freedom from angina, angina frequency and stability, measures of physical limitation, treatment satisfaction and quality of life for 6–24 months, the benefit being attenuated after 36 months.[54] The benefit from PCI was greatest among patients with severe and frequent angina. The findings have to be interpreted in the light of the considerable cross-over from medical therapy to subsequent revascularization and the fact that 25% of patients had missing follow-up health status assessments. Freedom from angina at one year was relatively low, with 66% in the PCI group of COURAGE compared with 81% in the PCI group of Fractional Flow Reserve Versus Angiography for Multi-vessel Evaluation (FAME-2),[50] a difference that may be explained by the near-exclusive use of DES, reducing the rate of re-stenosis, in the FAME-2 trial.

A meta-analysis of 14 RCTs enrolling 7818 patients reported a benefit on angina relief of PCI over medical treatment (OR 1.69; 95% CI 1.24–2.30).[55] The benefit of PCI appeared less pronounced in more recent RCTs, potentially resulting from greater use of evidence-based medical treatment. Notably, only the longest avail-

Indications for diagnostic testing in patients with suspected CAD and stable symptoms

	Asymptomatic[a]		Symptomatic						
			Probability of significant disease[b]						
			Low (<15%)		Intermediate (15–85%)		High (>85%)		
	Class[c]	Level[d]	Class[c]	Level[d]	Class[c]	Level[d]	Class[c]	Level[d]	Ref[e]
Anatomical detection of CAD									
Invasive angiography	III	A	III	A	IIb	A	I	A	50–52,54
CT angiography[f,g]	III	B	III	C	IIa	A	III	B	57–62
Functional test									
Stress echo	III	A	III	A	I	A	III	A	63–65
Nuclear imaging	III	A	III	A	I	A	III	A	60,66–70
Stress MRI	III	B	III	C	I	A	III	B	71–75
PET perfusion	III	B	III	C	I	A	III	B	67,69,70,76,77
Combined or hybrid imaging test									
	III	C	III	C	IIa	B	III	B	78–83

CONVENTIONAL WISDOM

Assunti terapeutici nel management della CAD stabile:

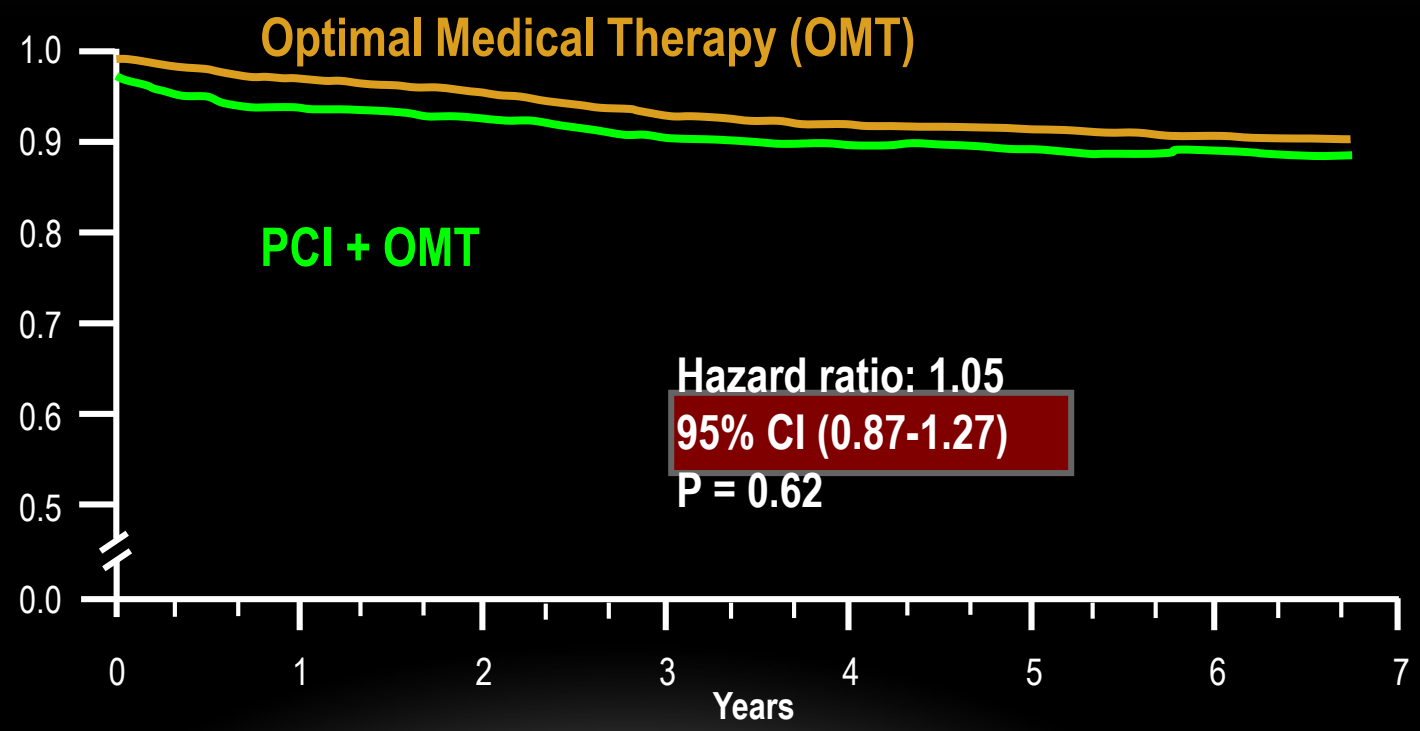
- Patients with symptomatic CAD and chronic angina who have significant coronary stenoses "need" revascularization

- Revascularization is required to improve prognosis, particularly if reversible ischemia is demonstrated

- PCI is less invasive than CABG surgery (i.e., is safer) and, therefore, should be selected

NON SOLO LA RIVASCOLARIZZAZIONE NEI PAZIENTI CON CAD STABILE NON MIGLIORA SIGNIFICATIVAMENTE PROGNOSI

SURVIVAL FREE OF DEATH FROM ANY CAUSE AND MYOCARDIAL INFARCTION IN THE COURAGE TRIAL



Number at Risk

Med Therapy	1138	1017	959	834	638	408	192	30
PCI	1149	1013	952	833	637	417	200	35

CONTROVERSIES IN IMAGING

Does Ischemia Burden in Stable Coronary Artery Disease Effectively Identify Revascularization Candidates?

Ma anche che l'ischemia reversibile sia in grado di selezionare i pazienti che beneficiano da rivascolarizzaizone rimane tutto da dimostrare

Ischemia Burden in Stable Coronary Artery Disease Does Not Effectively Identify Revascularization Candidates

Harmony R. Reynolds, MD; Michael H. Picard, MD; Judith S. Hochman, MD

Benefit of Revascularization in Patients With Stable Ischemic Heart Disease Is Controversial; A Better Method for Patient Selection Is Needed

Table 1. Summary of Large Randomized Trials Investigating the Role of Revascularization in Patients With Stable Ischemic Heart Disease

Year of Publication	Study	n	Ischemia-Based Entry Criteria	Revascularization Strategy	Medical Therapy	Primary Outcome	Secondary Outcomes	Ischemia Testing in Follow-Up
1994	Meta-analysis of randomized trials, CABG Trialists Collaboration[1]	2649	Angina (not required for all trials in meta-analysis)	CABG	Aspirin, nitrates (not for all trials)	All-cause mortality, lower in CABG group at 5–10 y	Angina relief better in CABG arms (CASS) through 5 y	Not performed
2007	COURAGE randomized trial[3]	2287	Site-determined abnormal stress test+70% stenosis or angina+80% stenosis	PCI	Aspirin, statin with target LDL<70, ACE inhibitor or ARB, antianginals	All-cause mortality or nonfatal MI, no difference between treatment groups at 3-6 years	Angina relief modestly better in PCI arm through year 3	PCI reduced ischemia better than medical therapy but no interaction between baseline ischemia severity and treatment effect
2009	BARI-2D randomized trial[4]	2368	Site-determined abnormal stress test or angina+70% stenosis	CABG or PCI	Aspirin, statin with target LDL<100, antihypertensives for BP target <130/80; diabetes management also tested in this trial	All-cause mortality, no difference between revascularization and medical therapy arms, no difference between CABG and medical therapy or PCI and medical therapy (stratified randomization) at 5.3 years	Composite of death, MI, stroke lower with revascularization in CABG stratum (n=763) Angina relief modestly better with revascularization in PCI stratum through year 1, CABG stratum through year 5	Revascularization reduced ischemia better than medical therapy
2014	FAME-2 randomized trial[5]	888	FFR≤0.8 in at least one vessel	FFR-guided PCI	Aspirin, statin with target LDL<70, β-blocker, ACE inhibitor or ARB	All-cause mortality, nonfatal MI or urgent revascularization, lower in FFR-guided PCI group at 2 years	No difference between treatment groups in death or MI	Not performed

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockade; BP, blood pressure; CASS, Coronary Artery Surgery Study; CABG, coronary artery bypass graft surgery; FAME-2, Fractional Flow Reserve–Guided PCI versus Medical Therapy in Stable Coronary Disease; FFR, fractional flow reserve; LDL, low-density lipoprotein; MI, myocardial infarction; and PCI, percutaneous coronary intervention.

L'ecostress è uno strumento potenzialmente utilissimo per studiare il rapporto tra ischemia reversibile e terapia di rivascolarizzazione successiva, un tema chiave

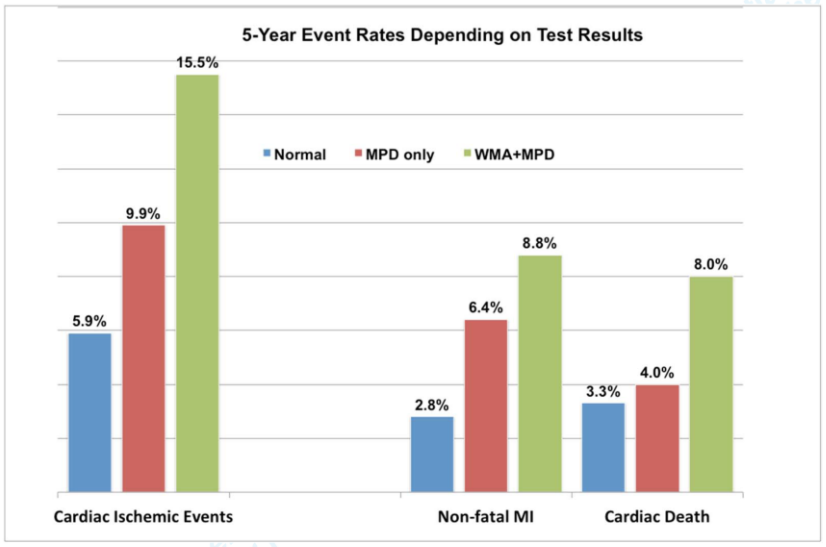


Figure 2.

Title: Effect of Coronary Revascularization on the Prognostic Value of Stress Myocardial Contrast Wall Motion and Perfusion Imaging.

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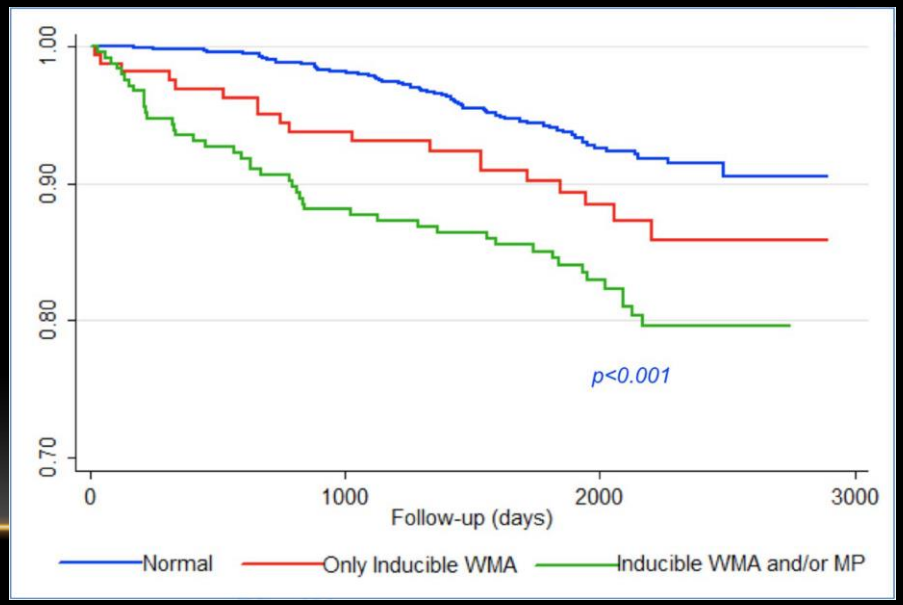
Le informazioni di prognosi sono utili, ma va detto che molti semplici score clinici possono far lo stesso e l'informazione più utile sarebbe invece quella capace di influenzare il management del paziente



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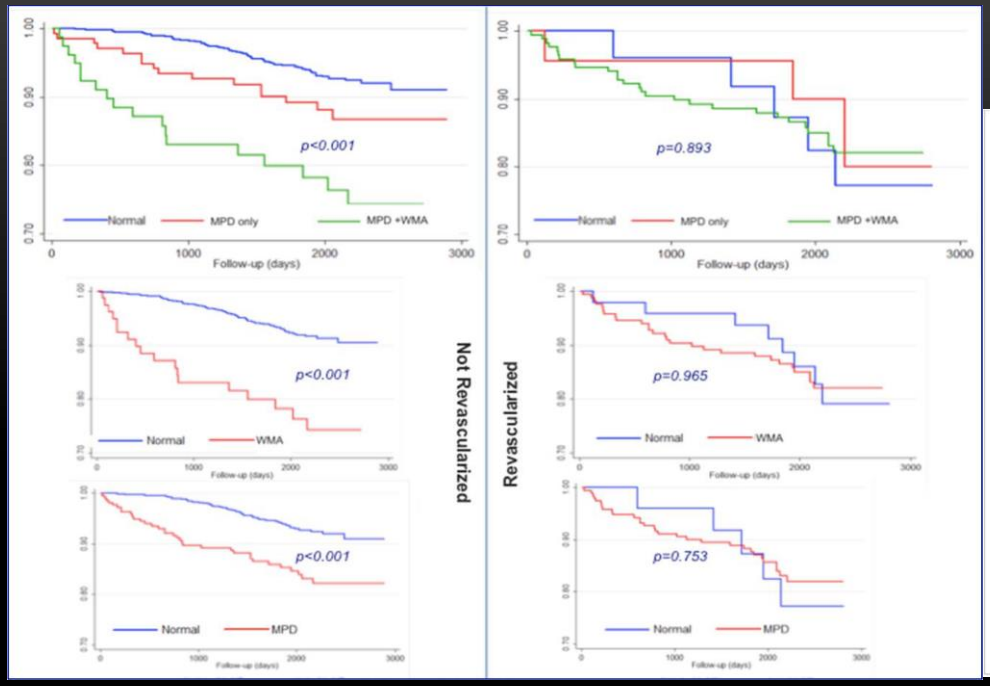

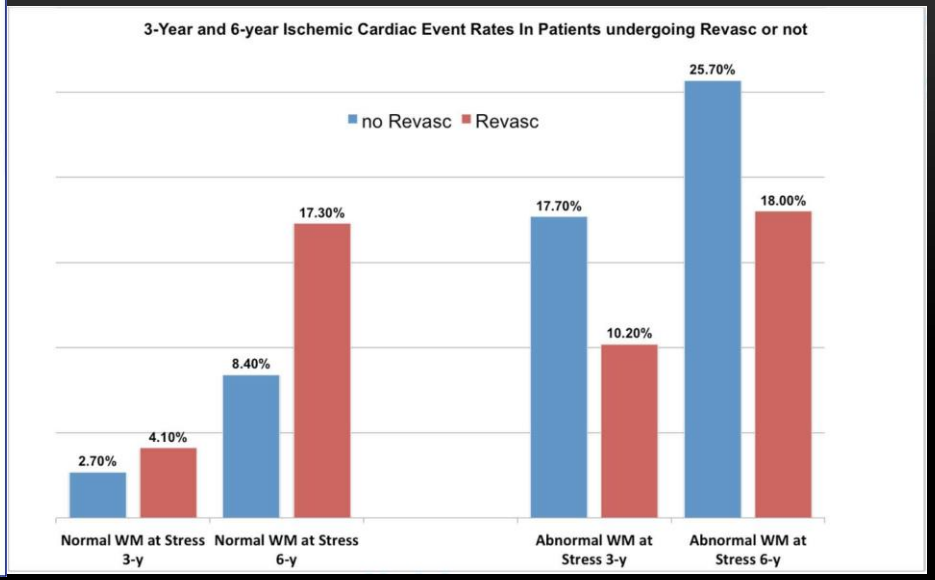

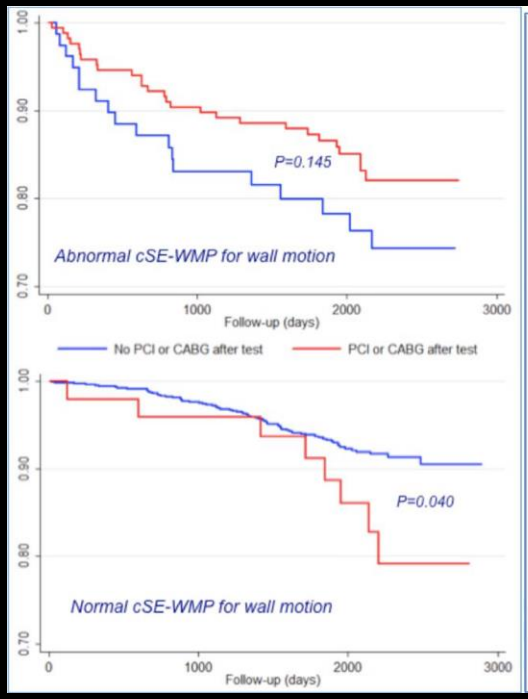

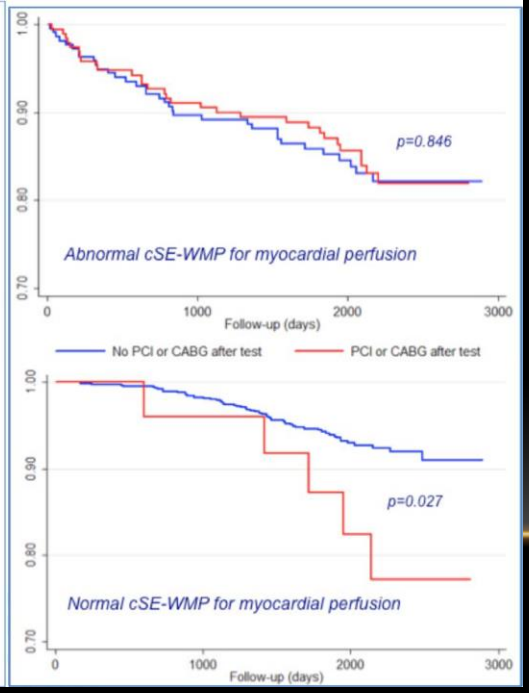

C'è un forte suggerimento verso il fatto che i pazienti con dimostrata ischemia reversibile (solo alterazioni di cinetica) sono quelli che beneficiano da rivascolarizzazione, ma studio osservazionale non-randomizzato

La rinascita della cinetica da sola non sensibile come metodica diagnostica, mainvece efficace come gatekeeper a rivascolarizzazione?

2017 submitted