UNIVERSITÀ DEGLI STUDI DI TORINO

AZIENDA OSPEDALIERO-UNIVERSITARIA
Città della Salute e della Scienza di Torino

TURIN
October
24th-26th
2019

Sala
Vittoria

THURSDAY October 24th 2019
Afternoon

BEATING …. ARTIFICIAL HEART IMPLANTATION

Chairpersons: C. Antona, M. Boffini, P. Centofanti

Expert Discussants: C. Comoglio, S. Frea, M. La Torre, A. Loforte,

31 GIORNATE CARDIOLOGICHE TORINESI

Cardiovascular Medicine

WHAT IS THE BEST IMAGING TOOL IN CARDIONCOLOGY?

Expert Discussants: E. Arboscello, B. Botto, E. Brignardello, P. Colonna, A. Fava, I. Parrini

17:20 Oncology and Cardiotoxicity M. Mistrangelo

17.30 Hematology and Cardiotoxicity P. Pregno

17:40 Radiotherapy and Cardiotoxicity M. Levis

17:50 What is the best imaging in cardioncology? M. Giorgi

Mauro GIORGI

S.C. CARDIOLOGIA U - OSP. MOLINETTE

CITTA' della SALUTE e della SCIENZA di TORINO

INTRODUCTION

- The **CANCER** is becoming a **CHRONIC-DEGENERATIVE DISEASE** and it puts us against **NEW CHALLENGES**
- **CARDIOTOXICITY** is a phenomenon bound to **INCREASE**
- CARDIOTOXICITY doesn't have a **TIME LIMIT** and can appear even **AFTER MANY YEARS** from the beginning of the treatment → **LONGTERM SURVEILLANCE**
- Potential **NEW TREATMENTS** that **may have cardiotoxic effects**

Consequence of a wrong management

The **inability** to predict the long-term consequences of cancer treatment associated cardiovascular side effects leads to:

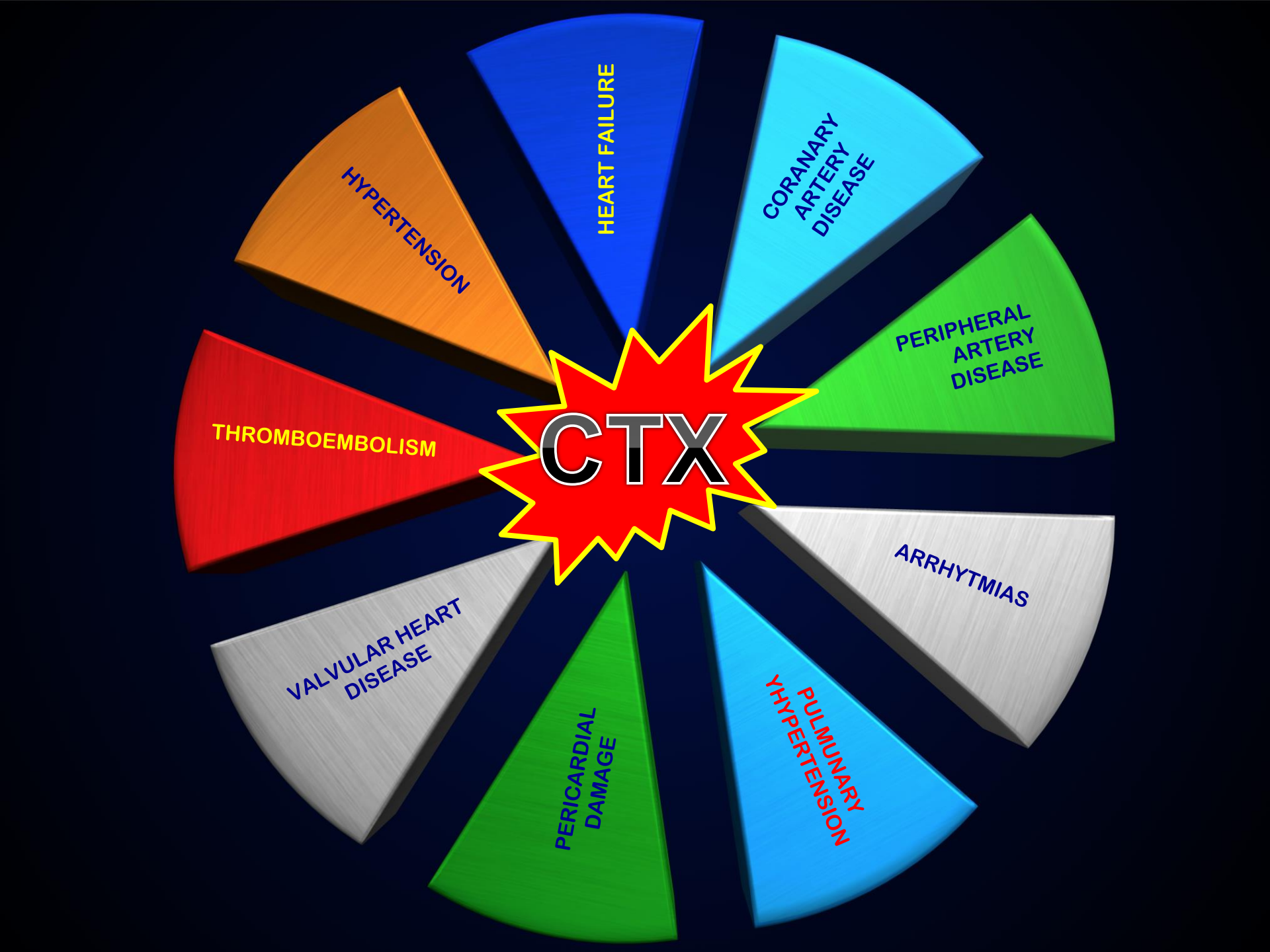
- **under-diagnosis → failure to prevent adverse events**

- **over-diagnosis → inappropriate interruption of a potentially lifesaving cancer treatment**

TABLE 83–3 Cardiotoxicity of Antineoplastic Agents

Implicated Agent	Comments
Anthracyclines	
Doxorubicin or daunorubicin	CHF at cumulative doses above 450 mg/m^2, arrhythmias
Mitoxantrone, idarubicin	CHF, decreases in left ventricular ejection fraction
Alkylating agents	
Cyclophosphamide	Produces a hemorrhagic myopericarditis 1-2 weeks after marrow transplant doses
Busulfan	Endocardial fibrosis
Cisplatin	Acute myocardial ischemia
Other cytotoxics	
Paclitaxel (Taxol)	Exacerbates anthracycline-associated CHF, bradycardia
5-Fluorouracil	Angina/myocardial infarction
Vincristine, vinblastine, vinorelbine (Navelbine)	Myocardial infarction
Biologics	
Trastuzumab (Herceptin)	Exacerbates anthracycline-associated CHF
Interferons	Exacerbates underlying cardiac disease
Interleukin-2	Acute myocardial injury, ventricular arrhythmias, hypotension
Hormones	
Megestrol (progestin)	Cardiomyopathy
Estramustine (androgen antagonist [Emcyt])	Myocardial infarction, CHF
Goserelin (gonadotropin-releasing hormone analog [Zoladex])	Myocardial infarction, CHF
Diethylstilbestrol (estrogen)	Myocardial infarction
Toremifene (antiestrogen [Fareston])	Myocardial infarction
Bicalutamide (antiandrogen [Casodex])	Angina, CHF, myocardial infarction
All-*trans*-retinoic acid	Myocardial dysfunction, heart failure, fever, shortness of breath, pleural and pericardial effusions, pulmonary infiltrates, and peripheral edema
Hematopoietic growth factors	
Granulocyte macrophage colony-stimulating factor (sargramostim [Leukine])	Capillary leak syndrome
Antiemetic	
Granisetron	Sinus bradycardia, atrioventricular block and increased PR interval or a Wenckebach block (Mobitz I).

CHF = congestive heart failure.


HEART FAILURE
CORANARY ARTERY DISEASE
PERIPHERAL ARTERY DISEASE
ARRHYTMIAS
PULMUNARY YHYPERTENSION
PERICARDIAL DAMAGE
VALVULAR HEART DISEASE
THROMBOEMBOLISM
HYPERTENSION
CTX

The role of Imaging in Cardioncology

- The modern multi-modality imaging approach to anti-cancer therapy complications should be focused on the **early diagnosis and treatment** of cardiovascular complications in individual Patients.
- In this context, **echocardiography** is the **first-line** imaging
- The application of other imaging tools, mainly **CMR**, should be **modulated whenever needed**.

- The **same imaging modality** and/or biomarker assay should be used for **continued screening** throughout the treatment pathway.

- **Switching between modalities or assays is strongly discouraged**.

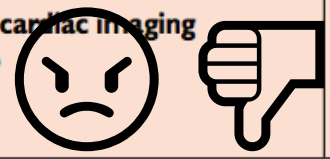
- Modalities and tests with the **best reproducibility** are preferred.

- Imaging modalities that provide **additional relevant clinical information** are preferred *(e.g. right ventricular function, pulmonary pressures, valvular function, pericardial evaluation)*.

- High quality **radiation-free imaging** is preferred, if available.

EUROPEAN SOCIETY OF CARDIOLOGY®

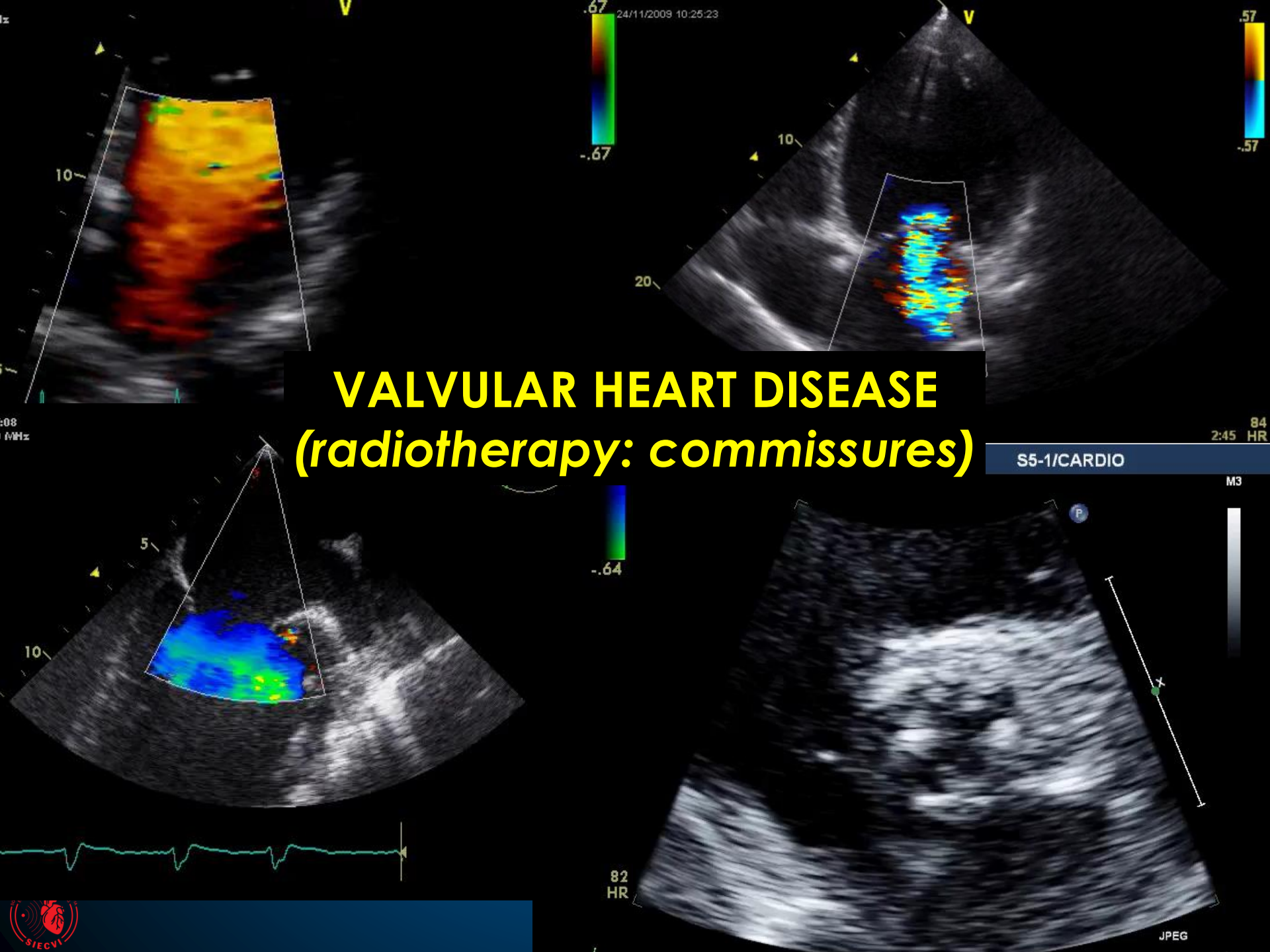
Table 6 **Proposed diagnostic tools for the detection of cardiotoxicity**

Technique	Currently available diagnostic criteria	Advantages	Major limitations
Echocardiography: **- 3D-based LVEF** **- 2D Simpson's LVEF** **- GLS**	• LVEF: >10 percentage points decrease to a value below the LLN suggests cardiotoxicity. • GLS: >15% relative percentage reduction from baseline may suggest risk of cardiotoxicity.	• Wide availability. • Lack of radiation. • Assessment of haemodynamics and other cardiac structures.	• Inter-observer variability. • Image quality. • GLS: inter-vendor variability, technical requirements.
Nuclear cardiac imaging (MUGA) 	• >10 percentage points decrease in LVEF with a value <50% identifies patients with cardiotoxicity.	• Reproducibility.	• Cumulative radiation exposure. • Limited structural and functional information on other cardiac structures. 
Cardiac magnetic resonance	• Typically used if other techniques are non-diagnostic or to confirm the presence of LV dysfunction if LVEF is borderlines.	• Accuracy, reproducibility. • Detection of diffuse myocardial fibrosis using T1/T2 mapping and ECVF evaluation.	• Limited availability. • Patient's adaptation (claustrophobia, breath hold, long acquisition times).
Cardiac biomarkers: **- Troponin I** **- High-sensitivity Troponin I** **- BNP** **- NT-proBNP**	• A rise identifies patients receiving anthracyclines who may benefit from ACE-Is. • Routine role of BNP and NT-proBNP in surveillance of high-risk patient needs futher investigation.	• Accuracy, reproducibility. • Wide availability. • High-sensitivity.	• Insufficient evidence to establish the significance of subtle rises. • Variations with different assays. • Role for routine surveillance not clearly established.

ACE-Is = angiotensin converting enzyme inhibitors; BNP = B-type natriuretic peptide; ECVF = extacellular volume fraction; GLS = global longitudinal strain; LV = left ventricular; LLN = lower limit of normality; LVEF = left ventricular ejection fraction; MUGA = multigated radionuclide angiography; NT-proBNP = N-terminal fragment B-type natriuretic peptide.

ROLE OF ECHOCARDIOGRAPHY

- **ECHOCARDIOGRAPHY** is the **quickest and most avaible imaging tool** in detecting cancer therapy related cardiotoxicity
- Echocardiography is the **cornerstone** in the cardiac imaging evaluation of Patients in **preparation for, during, and after cancer therapy**
- **ADVANTAGES**: wide availability, easy repeatability, versatility, lack of radiation exposure and safety in Patients with concomitant renal disease

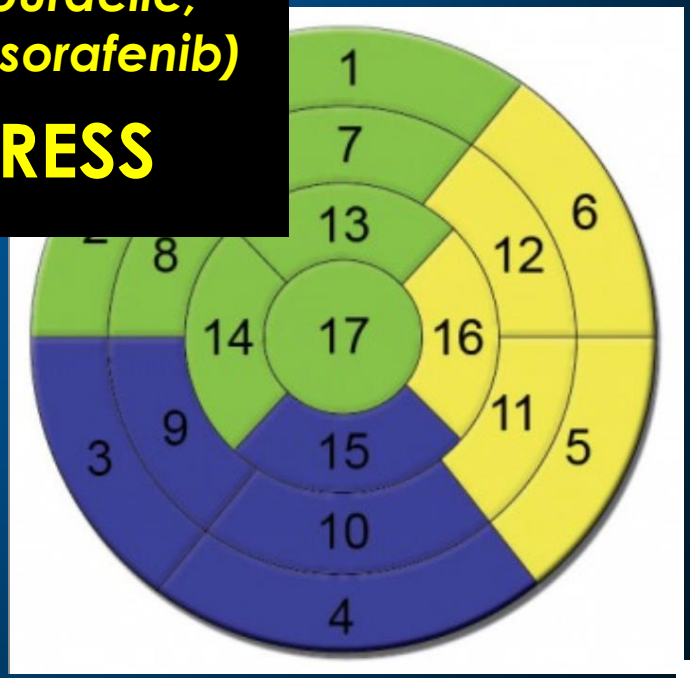


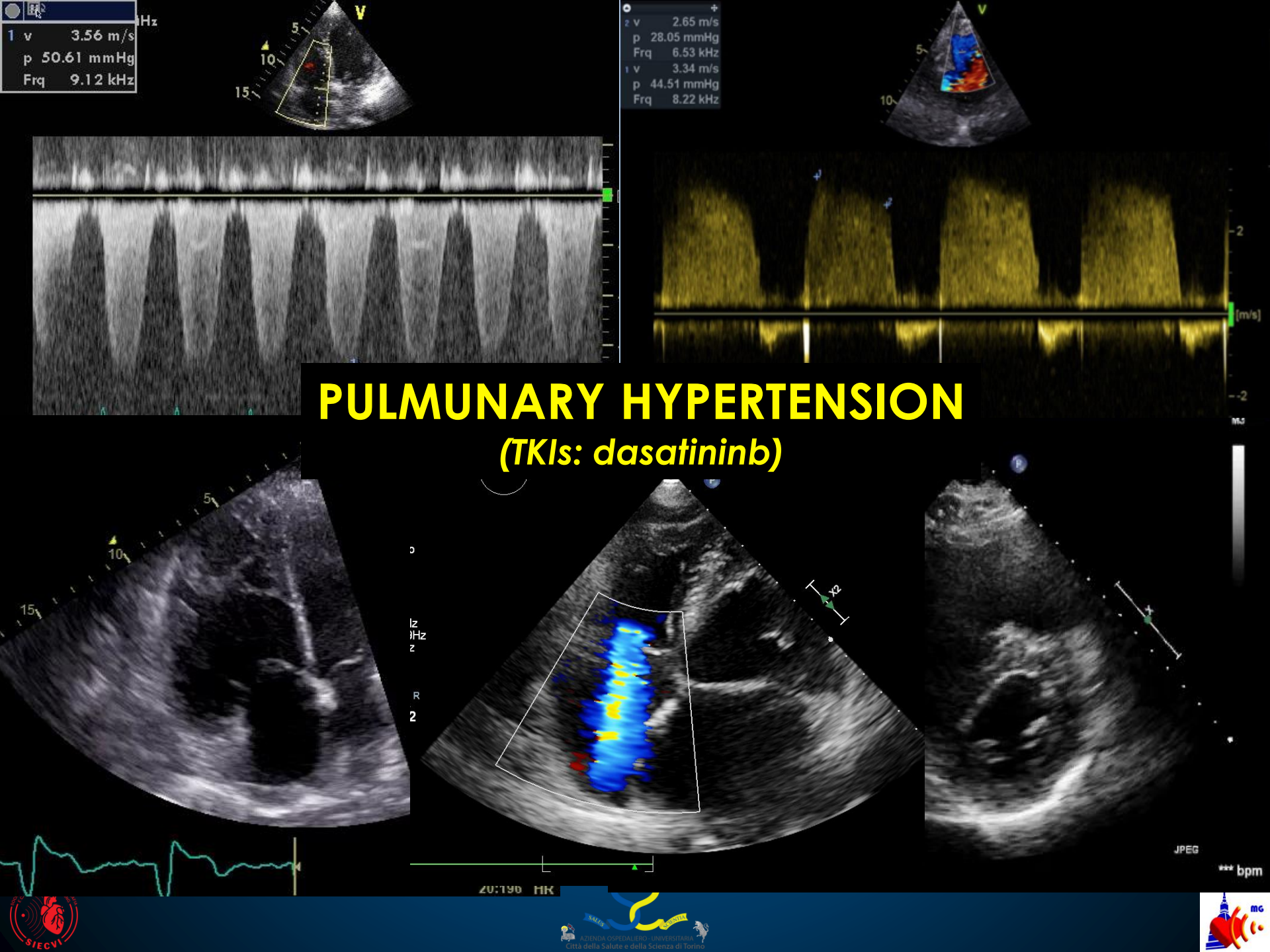
VALVULAR HEART DISEASE
(radiotherapy: commissures)

CORONARY ARTERY DISEASE

(capecitabina, 5-fluorouracile, bevacizumab, sunitinib, sorafenib)

WMSI - ECOSTRESS



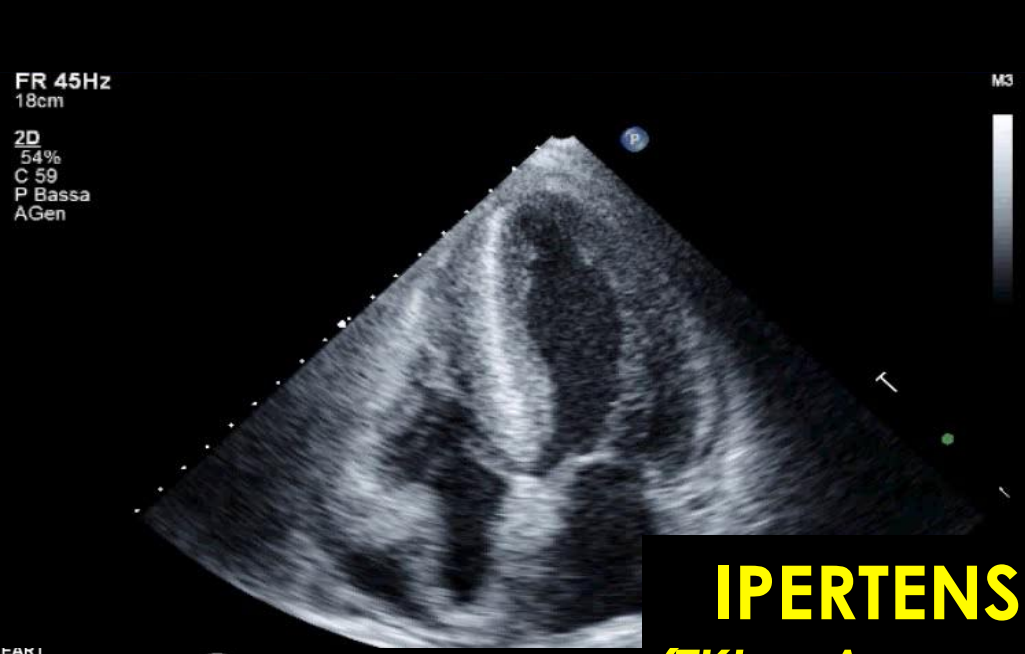


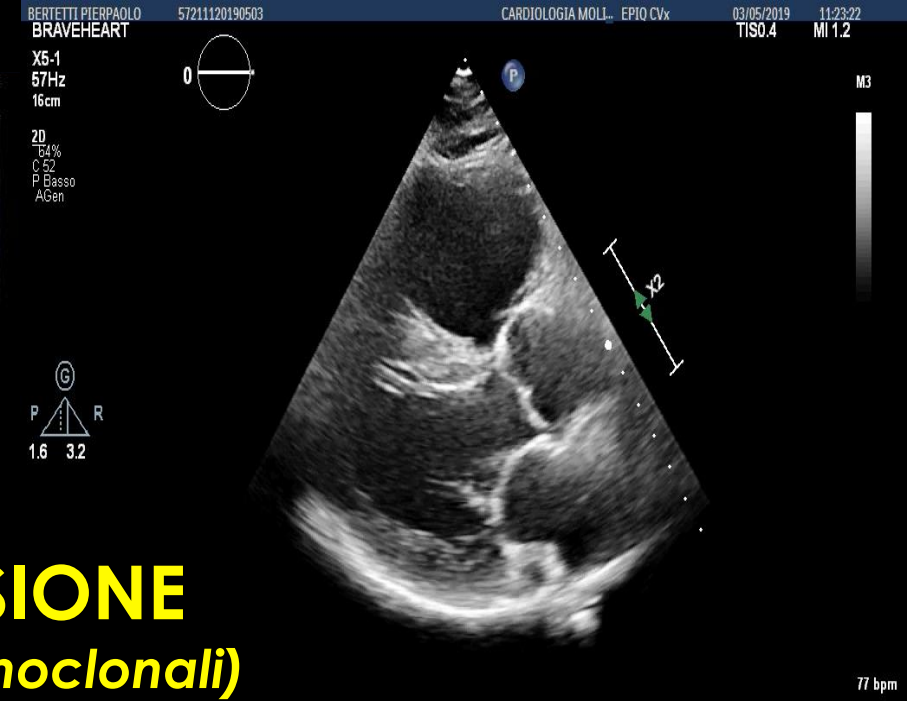
PULMUNARY HYPERTENSION

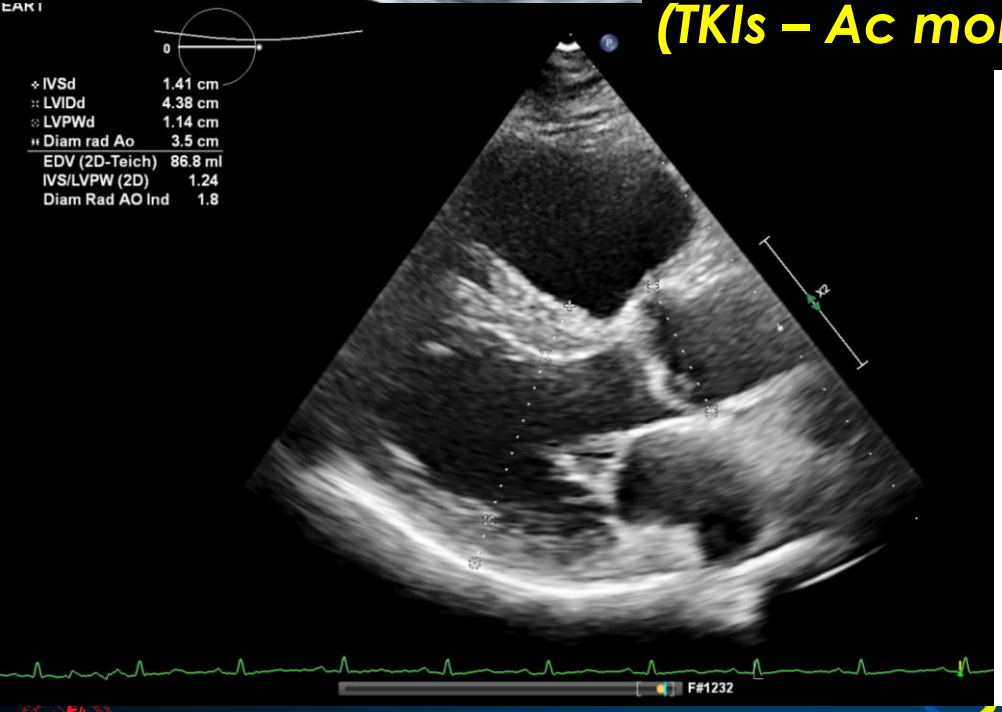
(TKIs: dasatininb)

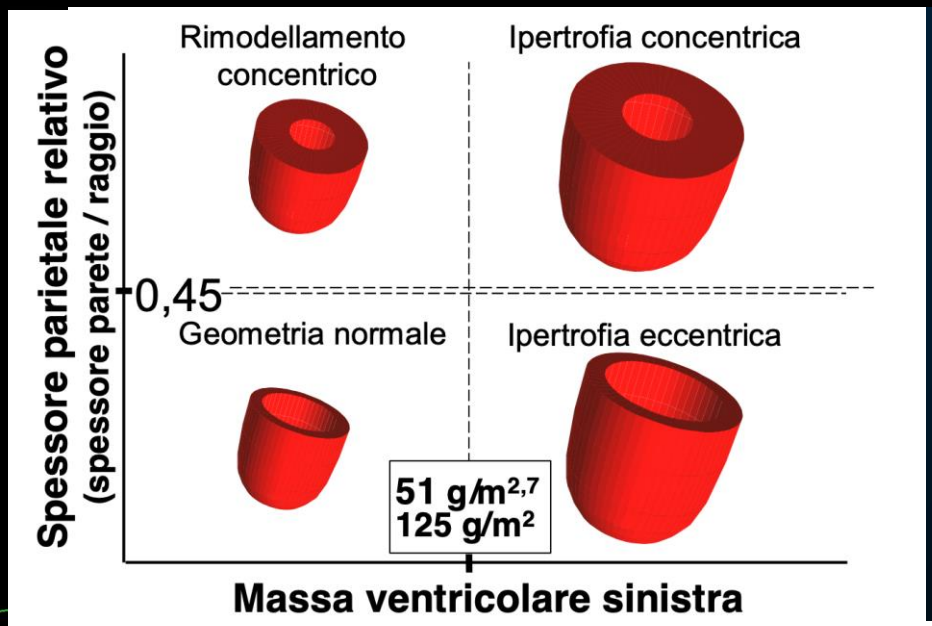
IPERTENSIONE

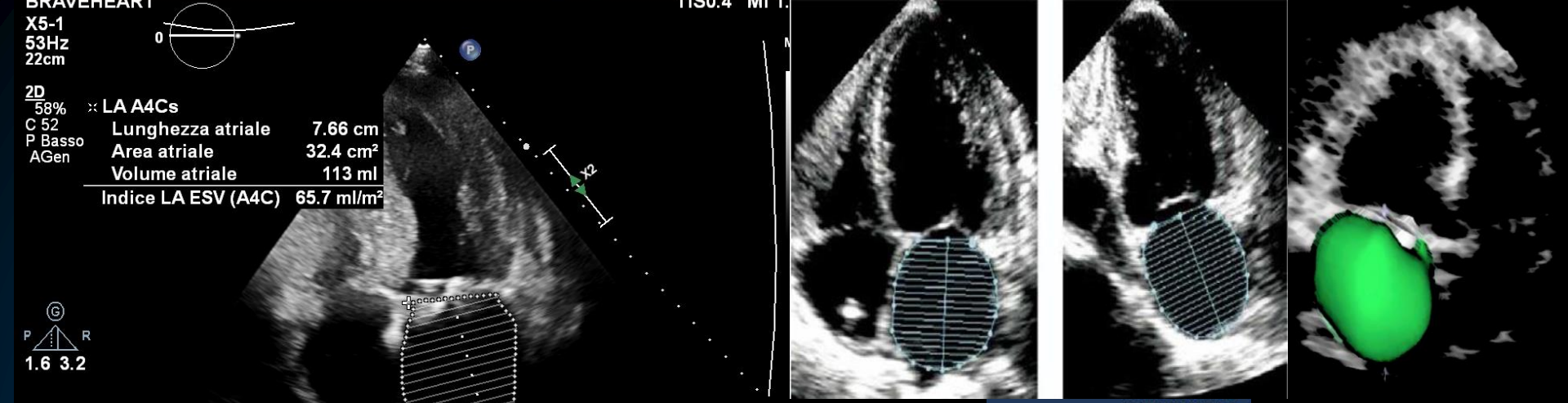
(TKIs – Ac monoclonali)





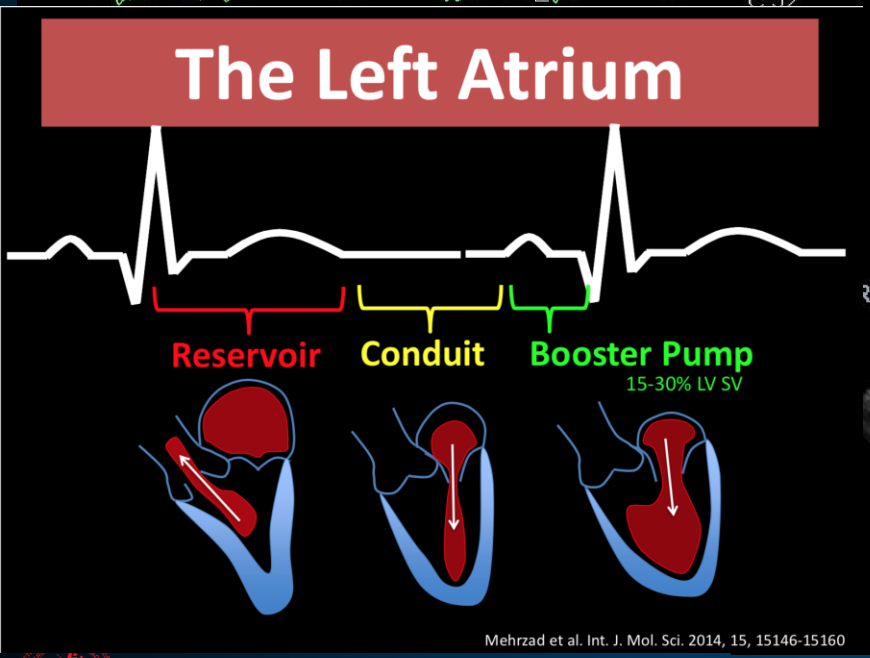




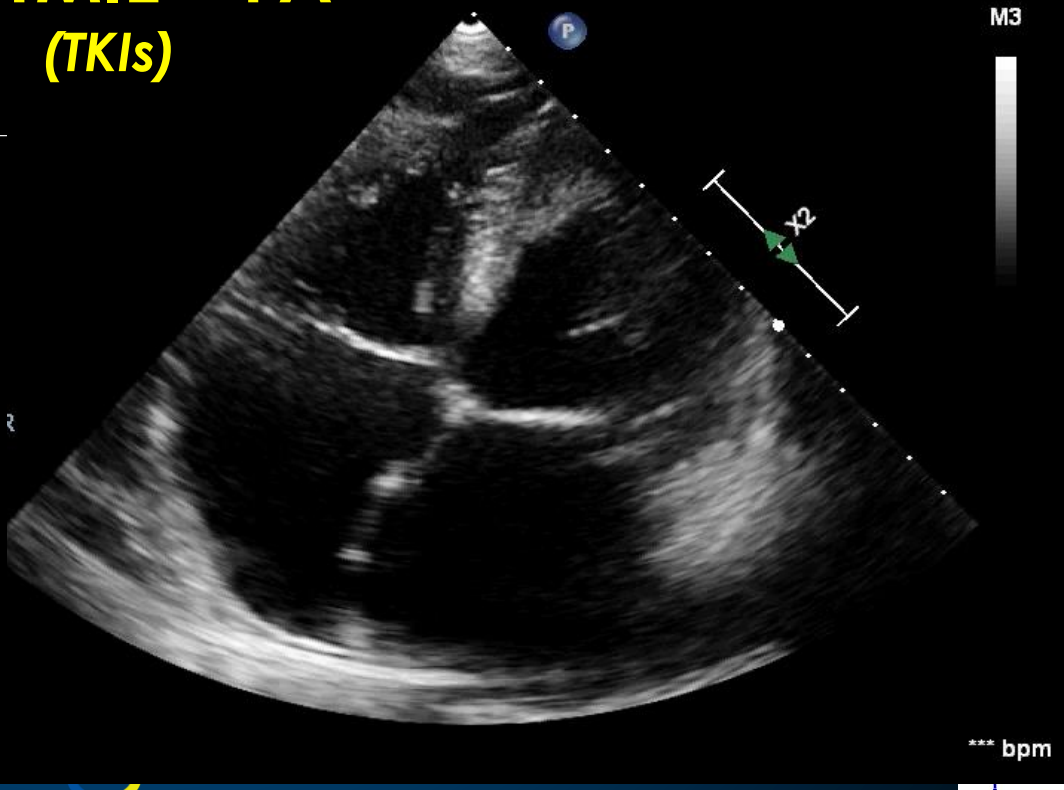


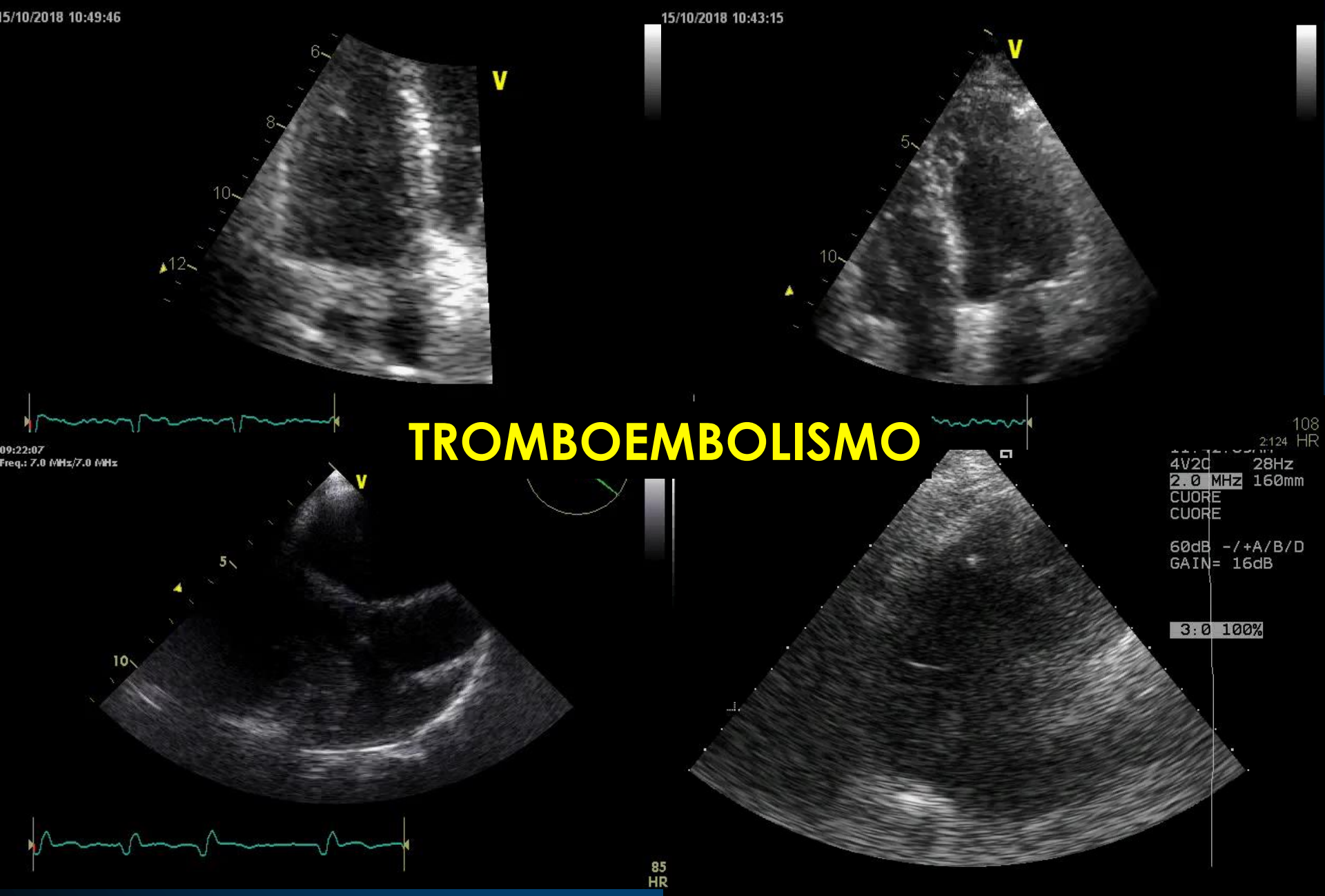
ARITMIE – FA

(TKIs)

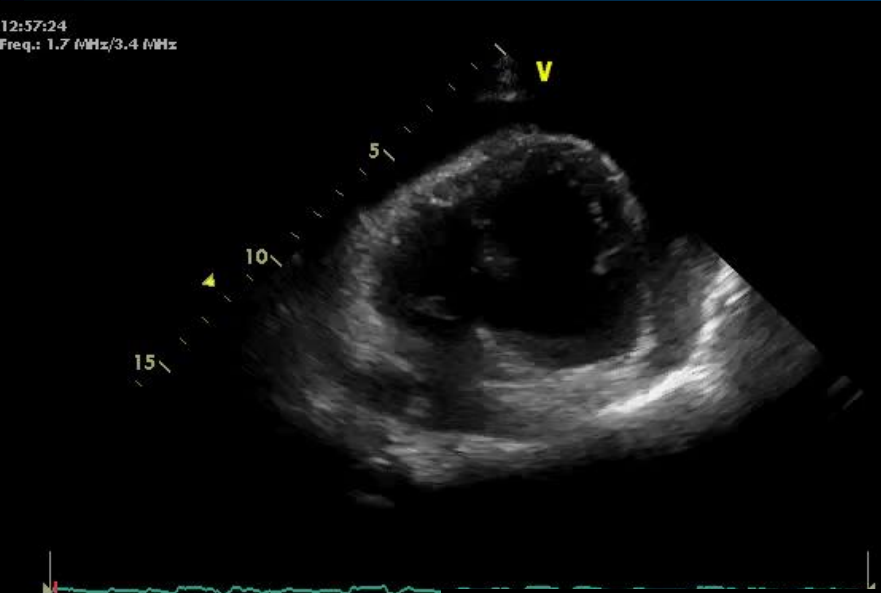


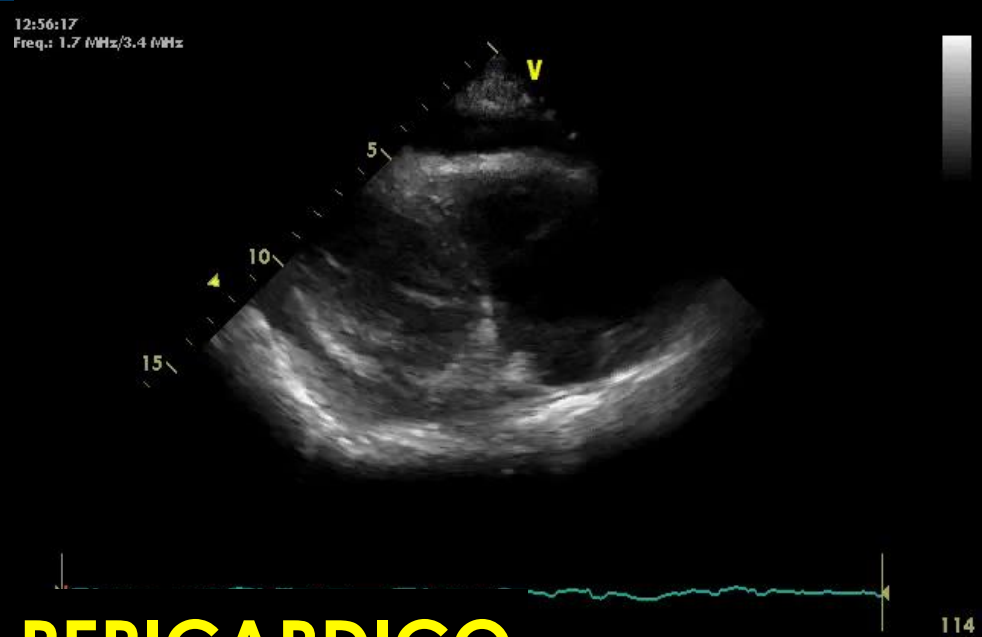
Mehrzad et al. Int. J. Mol. Sci. 2014, 15, 15146-15160

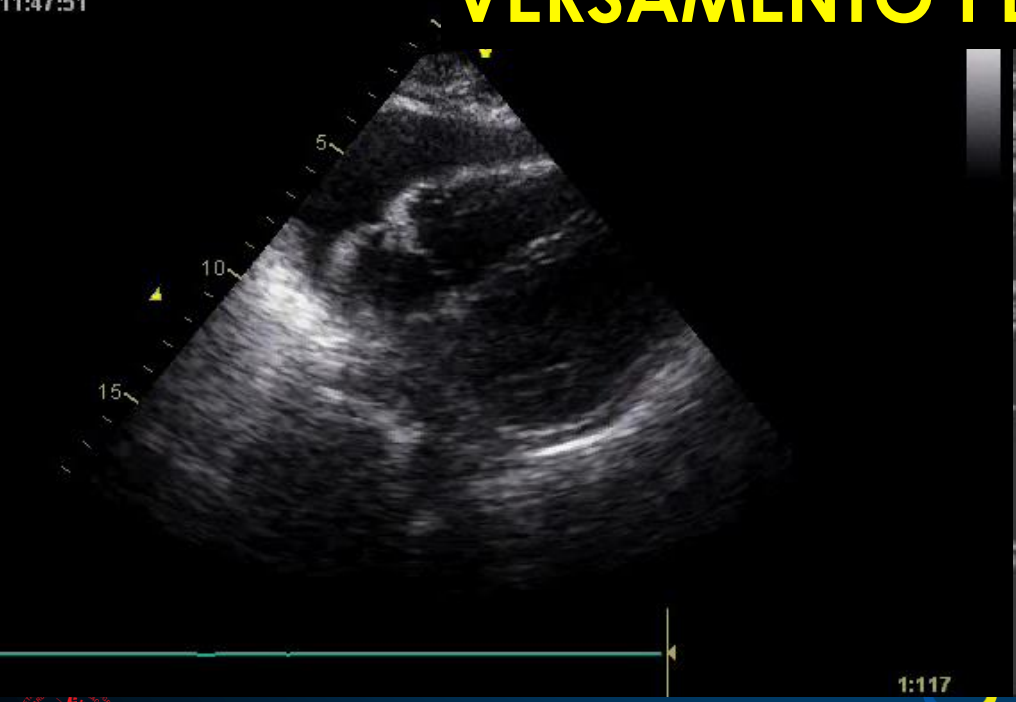


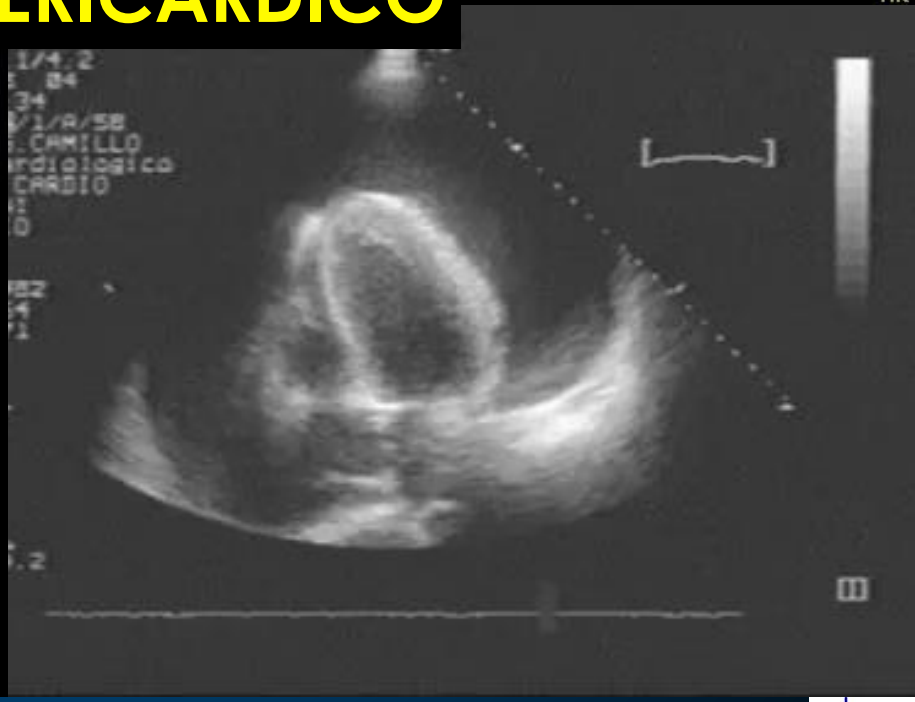

15/10/2018 10:49:46
15/10/2018 10:43:15
TROMBOEMBOLISMO
09:22:07
Freq.: 7.0 MHz/7.0 MHz
108
HR
2:124
4V2C 28Hz
2.0 MHz 160mm
CUORE
CUORE
60dB -/+A/B/D
GAIN= 16dB
3:0 100%
85
HR

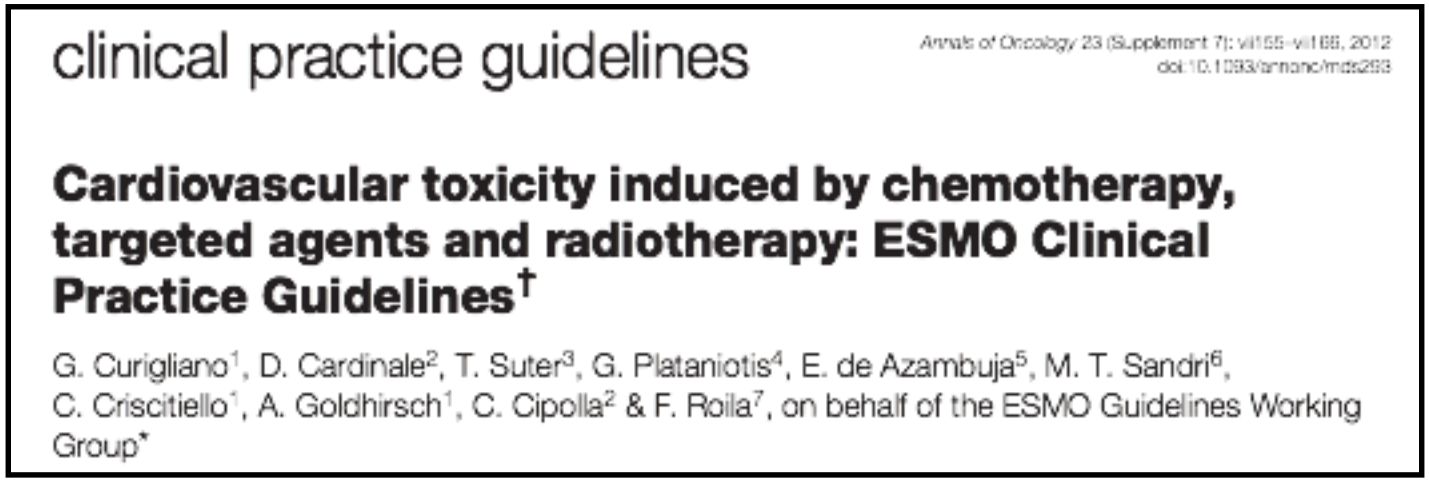
VERSAMENTO PERICARDICO











clinical practice guidelines

Annals of Oncology 23 (Supplement 7): vii155–vii166, 2012
doi:10.1093/annonc/mds293

Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO Clinical Practice Guidelines†

G. Curigliano[1], D. Cardinale[2], T. Suter[3], G. Plataniotis[4], E. de Azambuja[5], M. T. Sandri[6], C. Criscitiello[1], A. Goldhirsch[1], C. Cipolla[2] & F. Roila[7], on behalf of the ESMO Guidelines Working Group*

La **cardiotossicità** è caratterizzata da almeno uno tra:

-sintomi di scompenso cardiaco

-segni clinici di scompenso cardiaco (es. T3 o tachicardia)

-riduzione di EF di almeno 5% sotto i 55% con sintomi o segni di scompenso

-riduzione di EF del 10% sotto i 55% senza segni o sintomi associati

La FRAZIONE D'EIEZIONE: un campo minato !

BMJ Journals

Heart

Home / Archive / Volume 94, Issue 4

Editorial

Ejection fraction: a measure of desperation?

Charlotte H Manisty, Darrel P Francis

Author affiliations +

http://dx.doi.org/10.1136/hrt.2007.118976

Quali sono i limiti nella valutazione dell'EF ?

Left Ventricular Ejection Fraction

VARIABILITÀ dei "CUT OFF" di EF

	Normal	Mild	Moderate	Severe
2015	>52	51-41	40-30	<30
2005	>55	54-45	44-30	<30

LV Ejection Fraction

VARIABILITÀ dei "CUT OFF" di EF

Male

	Normal	Mildly	Moderately	Severely
LVEF	52-72	41-51	30-40	<30

Female

	Normal	Mildly	Moderately	Severely
LVEF	54-74	41-53	30-40	<30

DEFINIZIONI E LIMITI EF

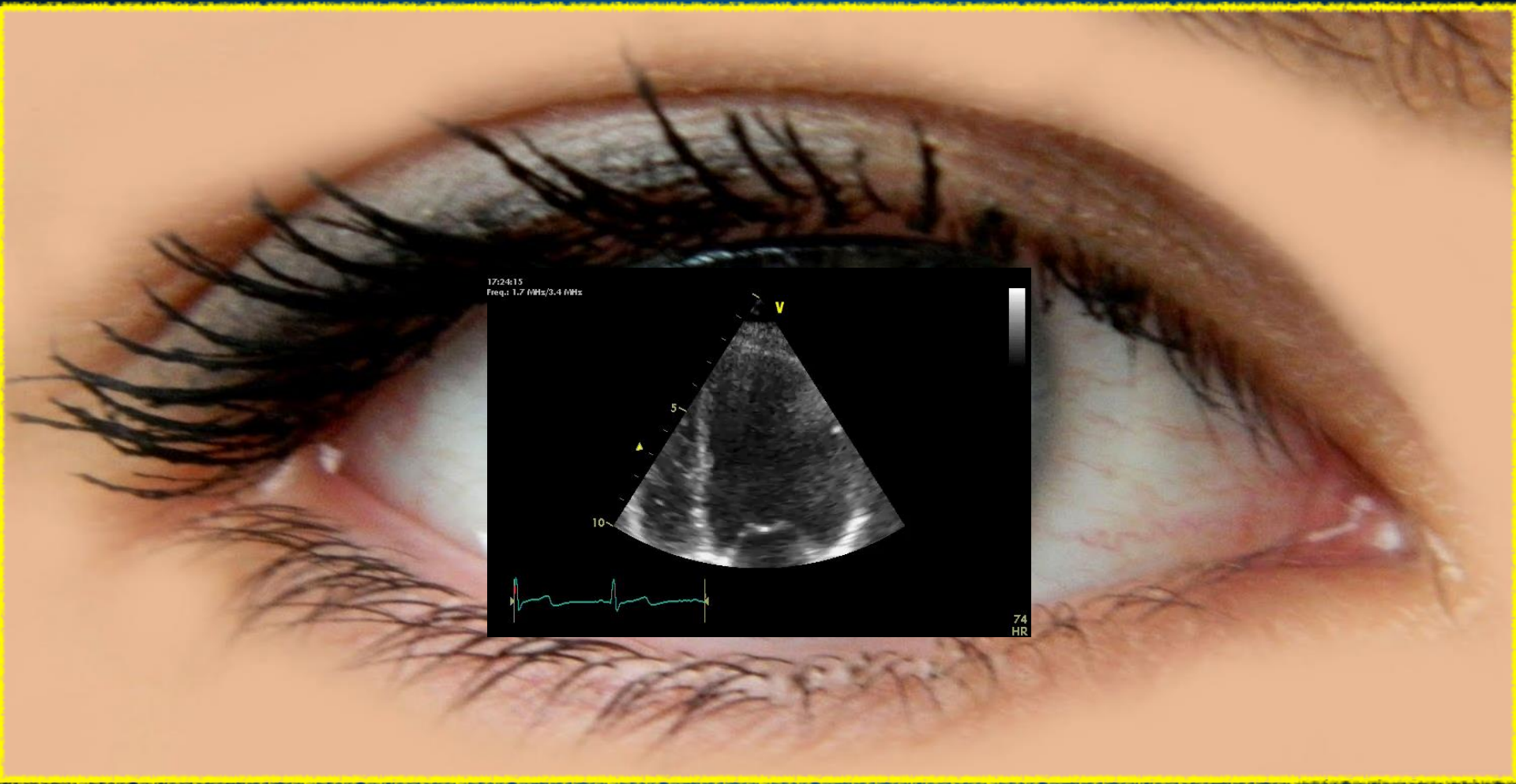
- Differenze di "**cut-off**" di normalità tra le diverse Guidelines:

  -ESC: **50%**

  -ESMO: **55%**

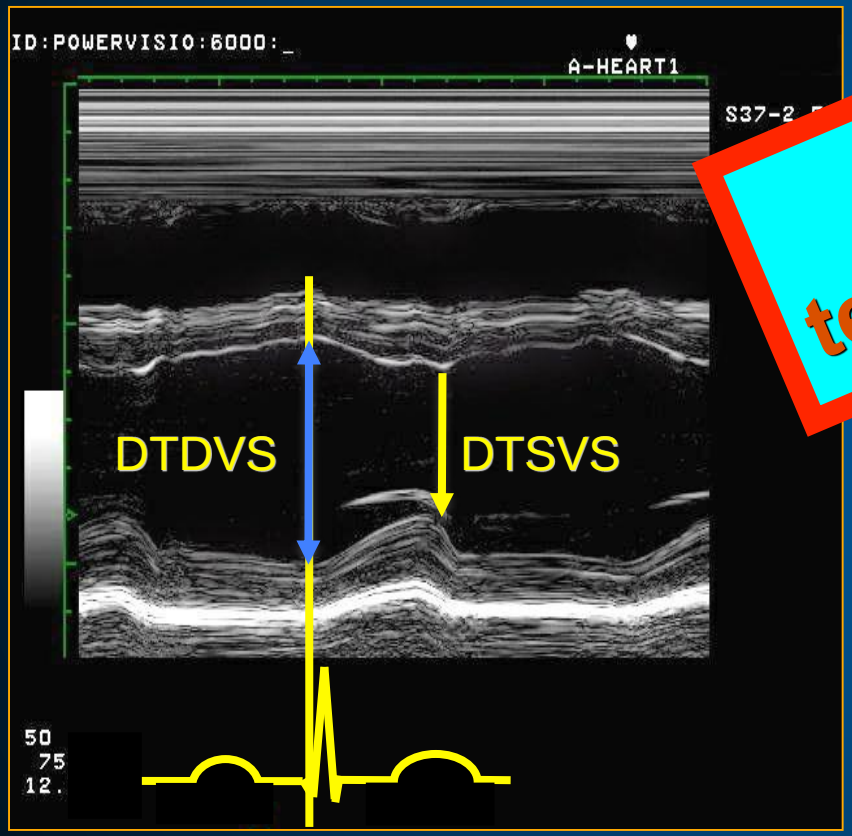
  -Expert consensus imaging ESC: **53%**

LIMITI dell'ECOCARDIOGRAFIA



Come deve essere valutata la frazione d'eiezione?

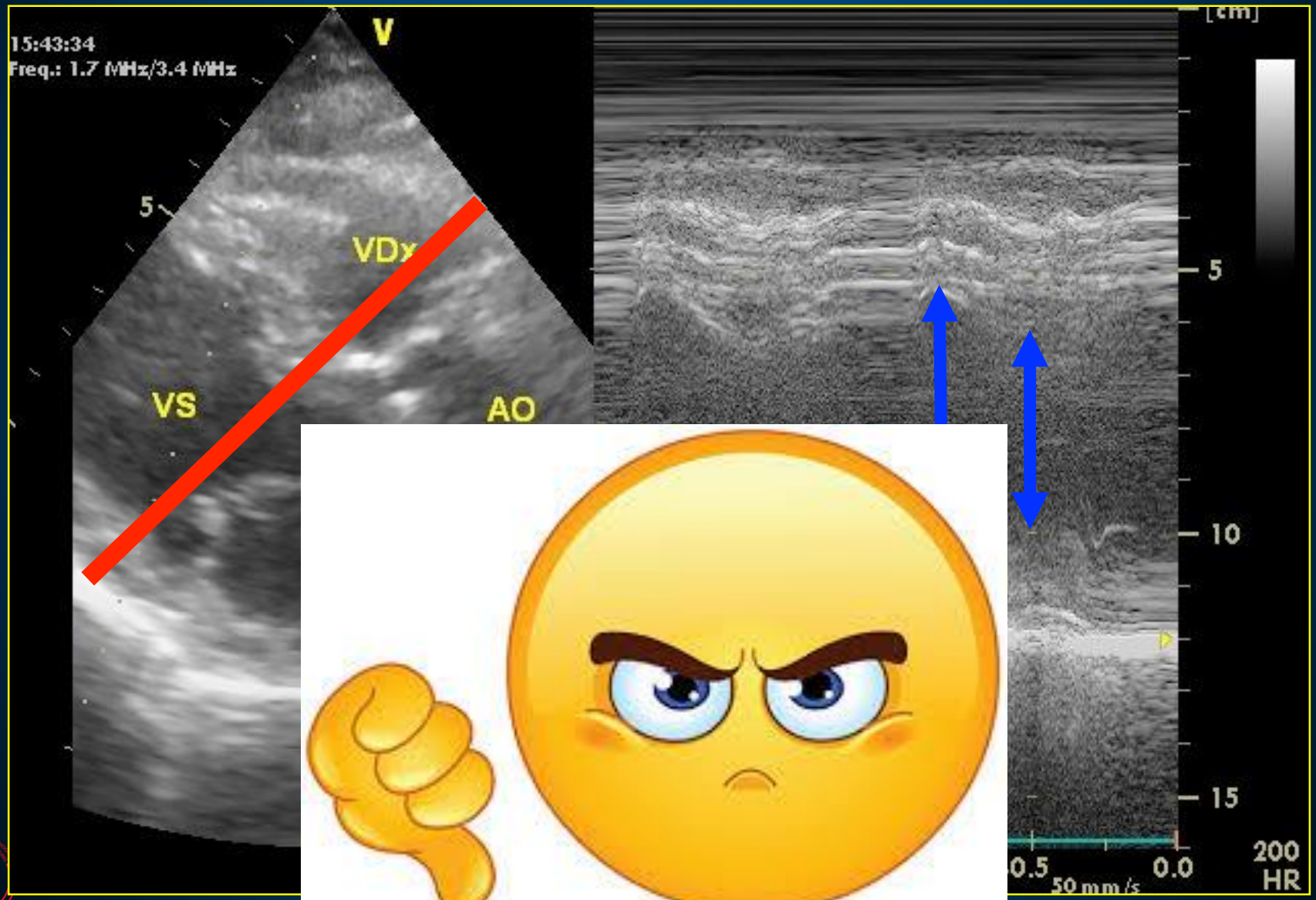
Fractional shortening o FS



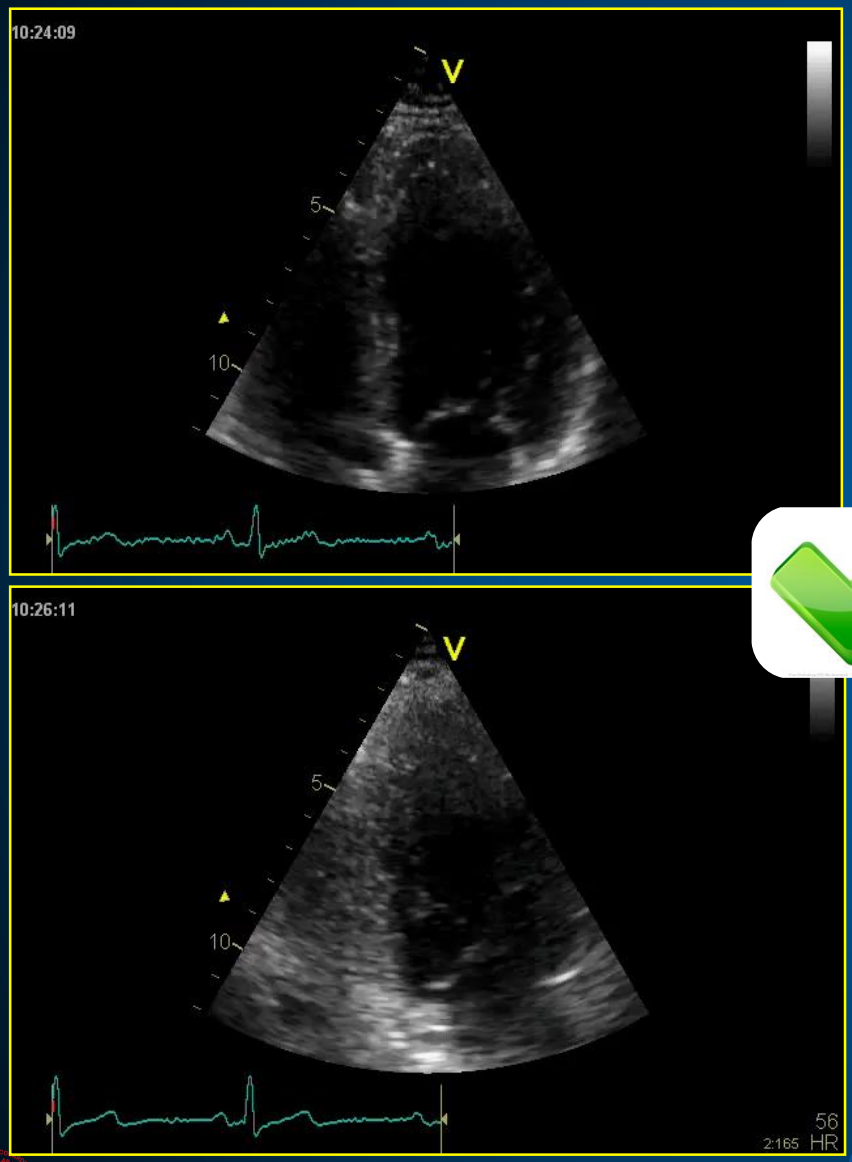
Misura imprecisa e terminologia confondente !

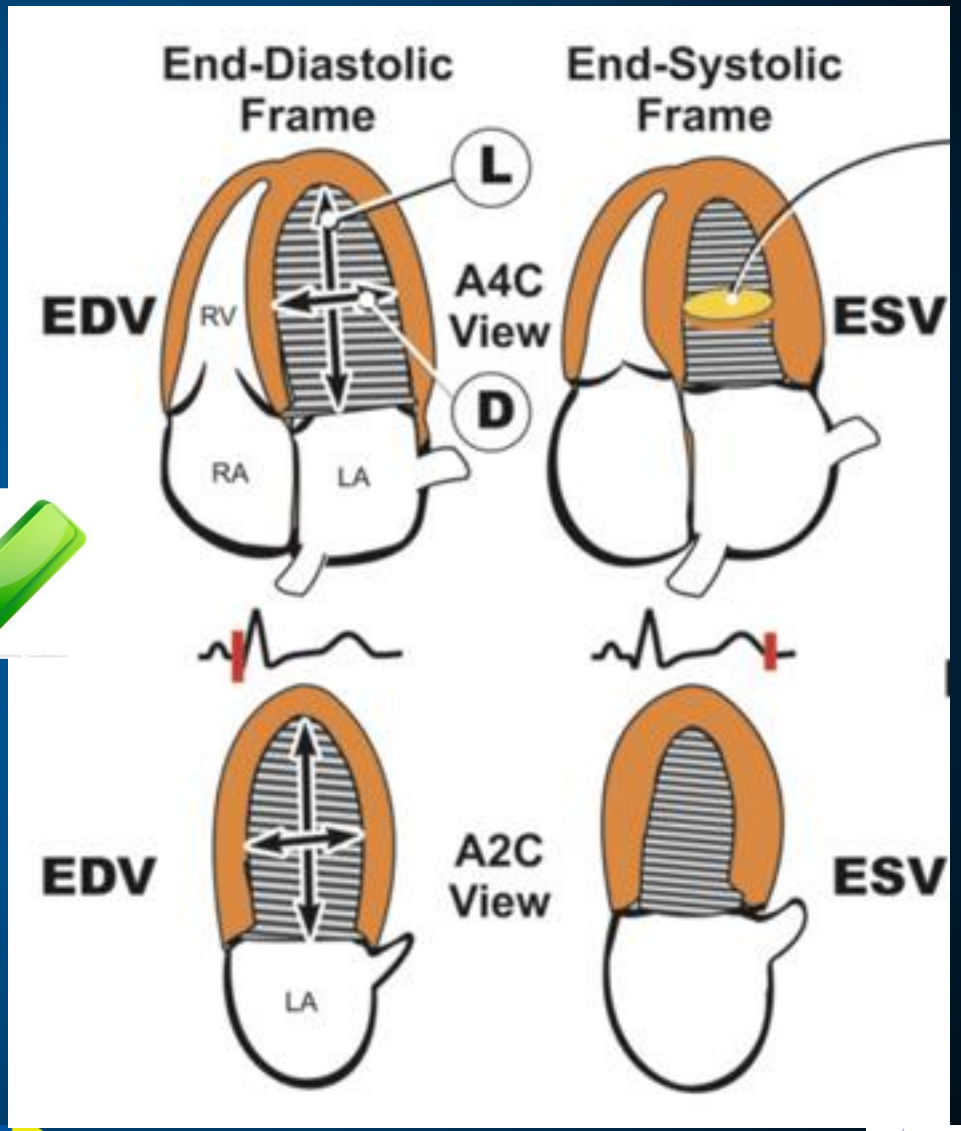
$$\frac{DTDVS - DTSVS}{DTD} \times 100\%$$

M-MODE: TEICHOLZ

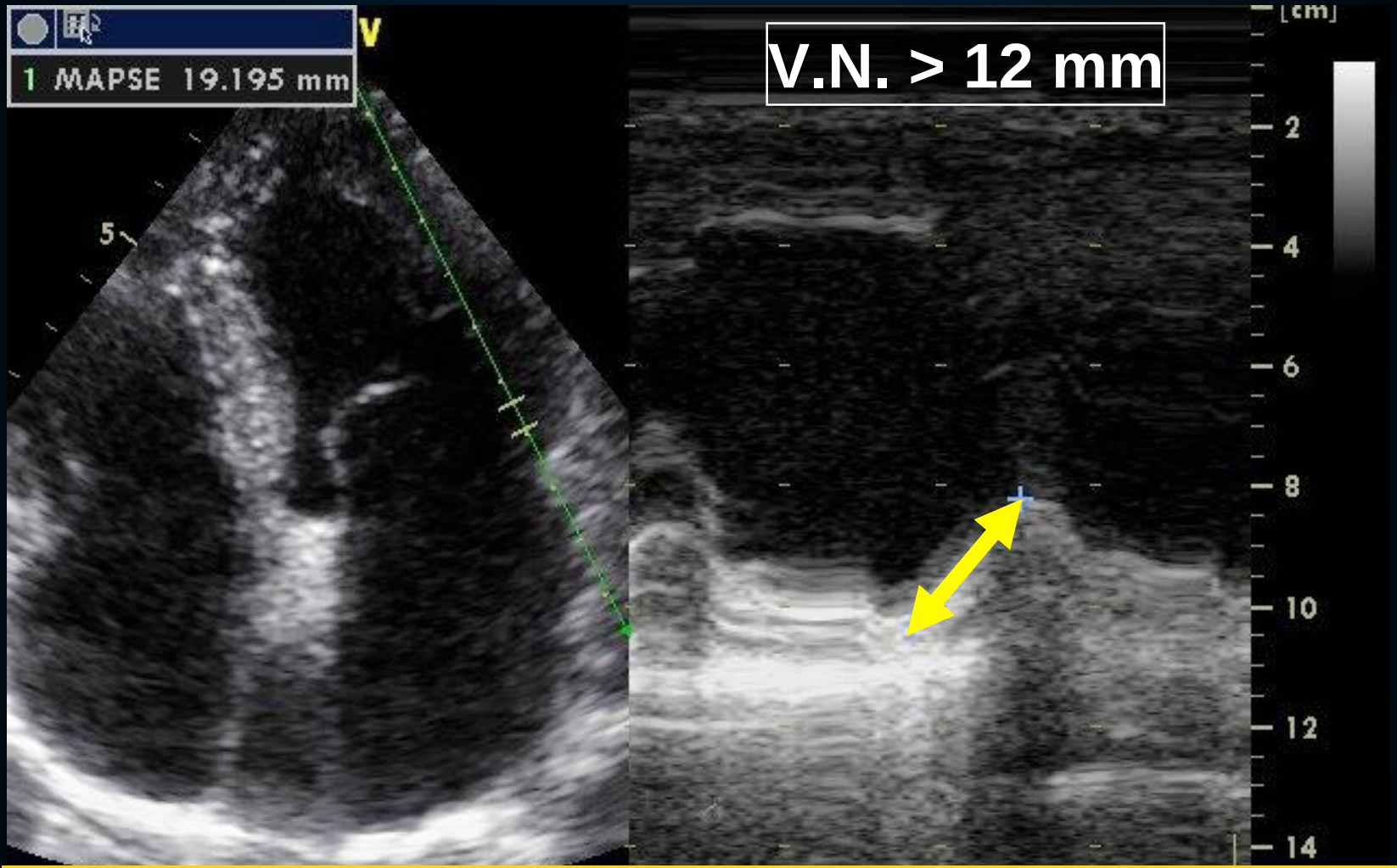


2D SIMPSON BIPLANO



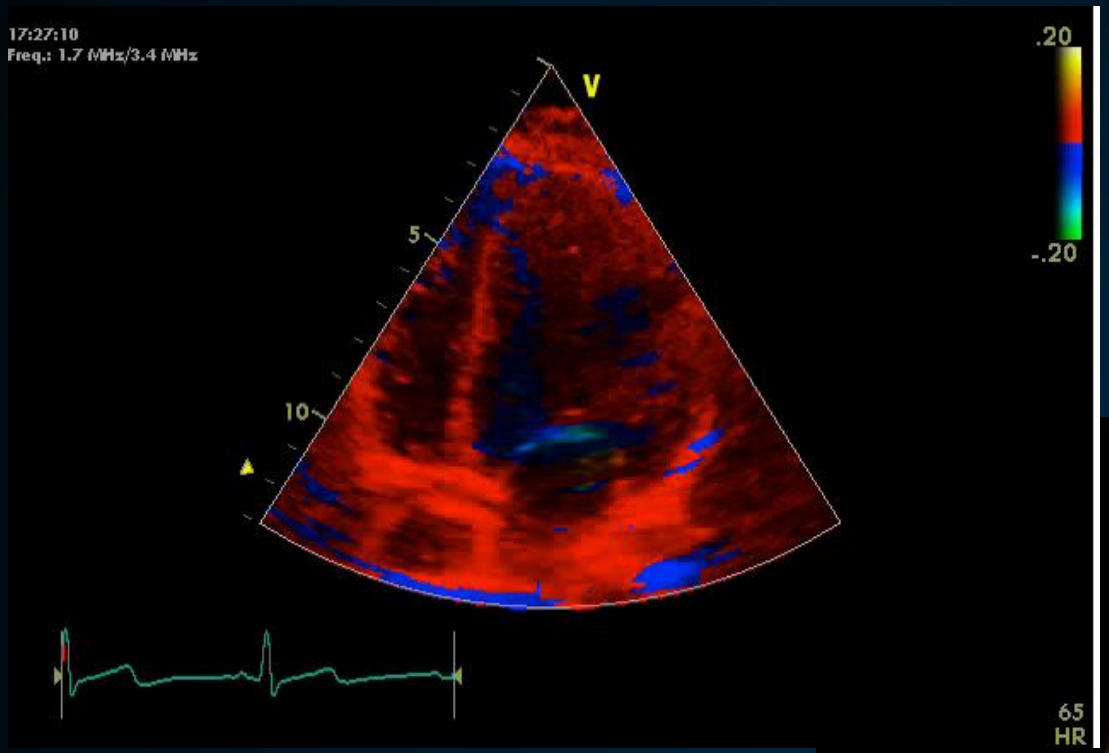


MAPSE

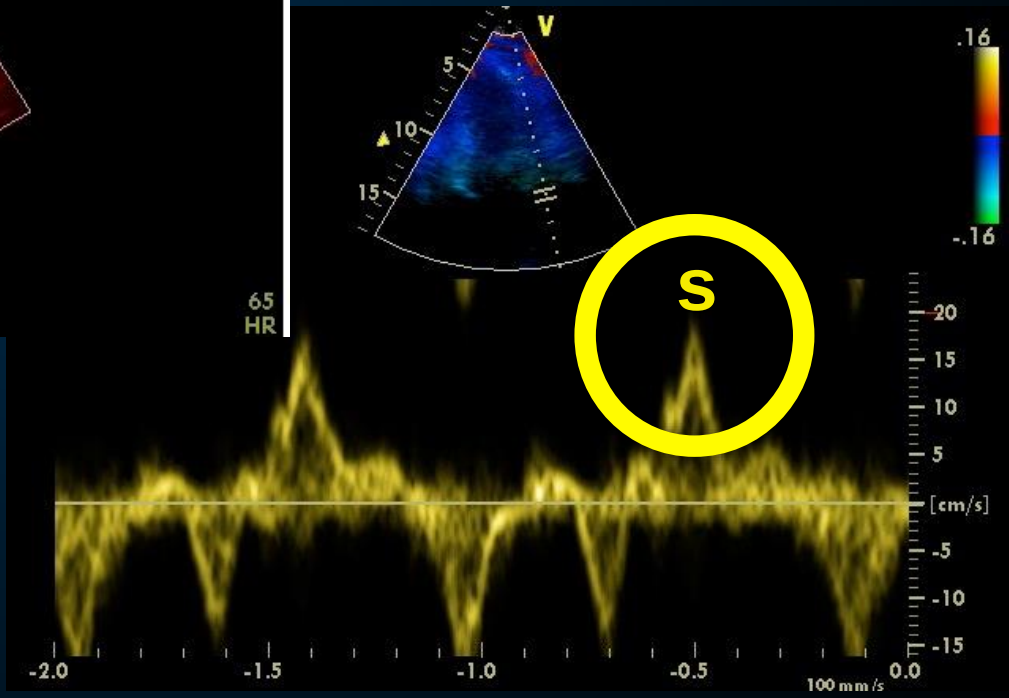


MAPSE = "**M**itral **A**nnular **P**lane **S**ystolic **E**xcursion"

DOPPLER TISSUTALE

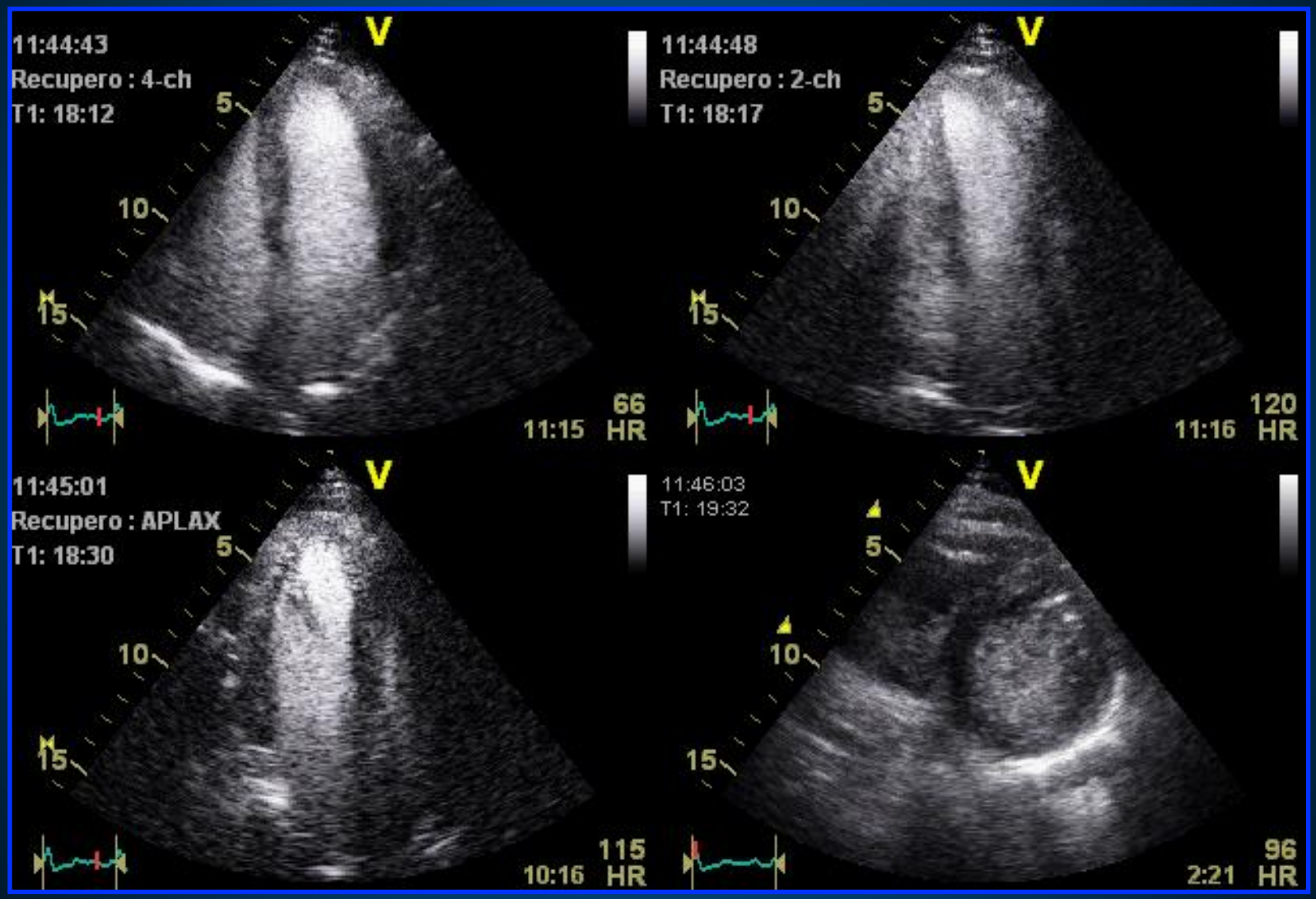


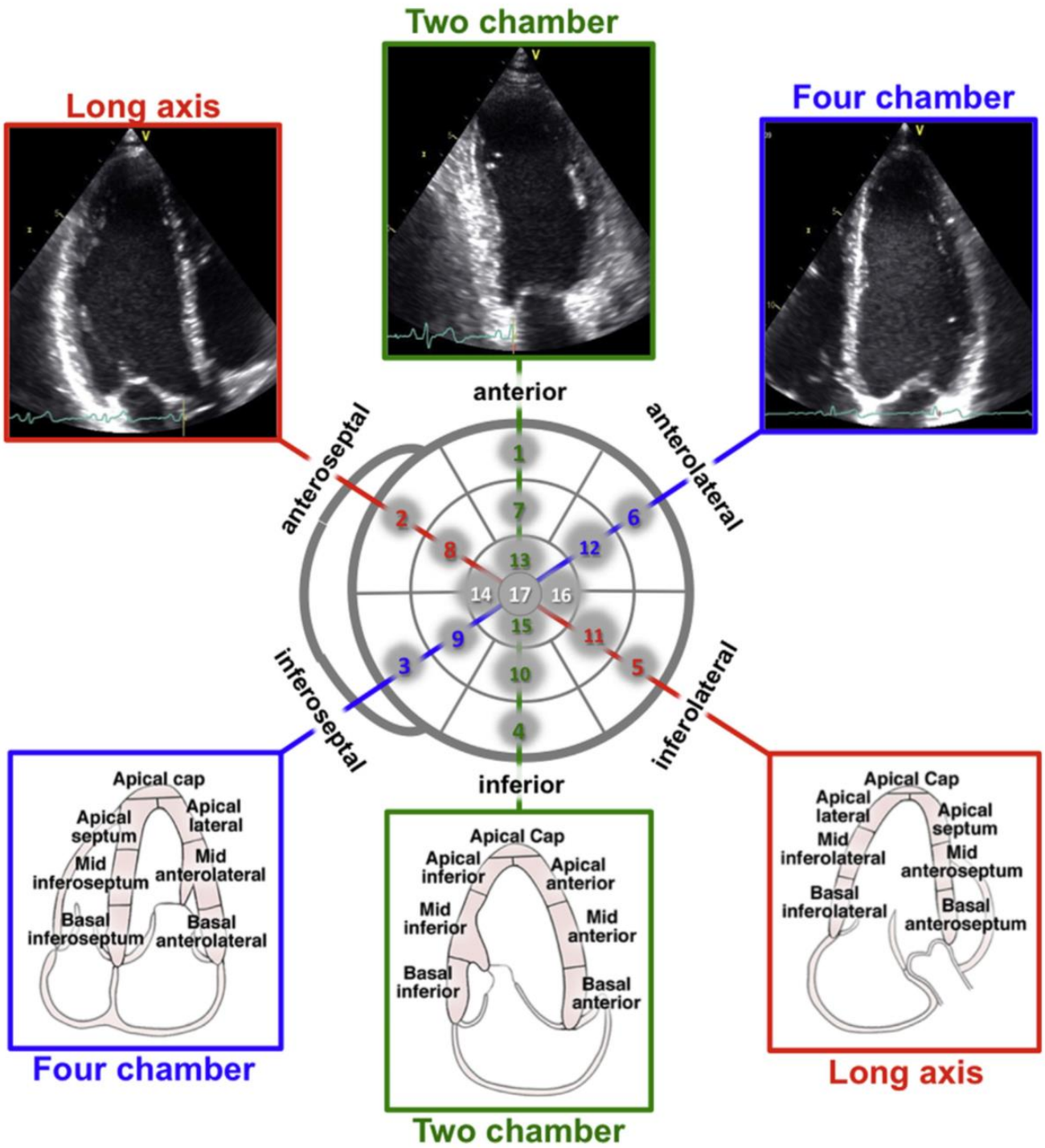
S2 ≧ 8 cm/s



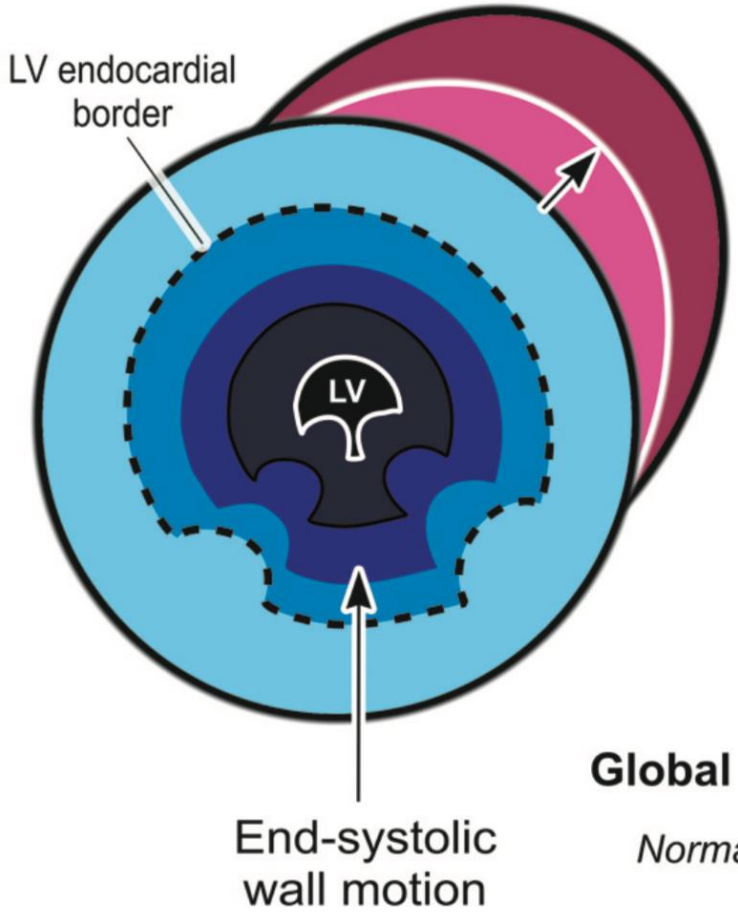
S1: evidente in ipertensione, ipertrofia, anziani, CMP ipocinetica, CAD

Opacificazione VS




Two chamber
Long axis
Four chamber
anterior
anteroseptal
anterolateral
inferoseptal
inferolateral
inferior
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
Apical cap
Apical septum
Apical lateral
Mid inferoseptum
Mid anterolateral
Basal inferoseptum
Basal anterolateral
Four chamber
Apical Cap
Apical inferior
Apical anterior
Mid inferior
Mid anterior
Basal inferior
Basal anterior
Two chamber
Apical Cap
Apical lateral
Apical septum
Mid inferolateral
Mid anteroseptum
Basal inferolateral
Basal anteroseptum
Long axis

WALL MOTION SCORE INDEX



WALL MOTION SCORE (WMS)

Aneurysmal	5
Dyskinetic	4
Akinetic	3
Hypokinetic	2
Normal	1
Hyperkinetic	

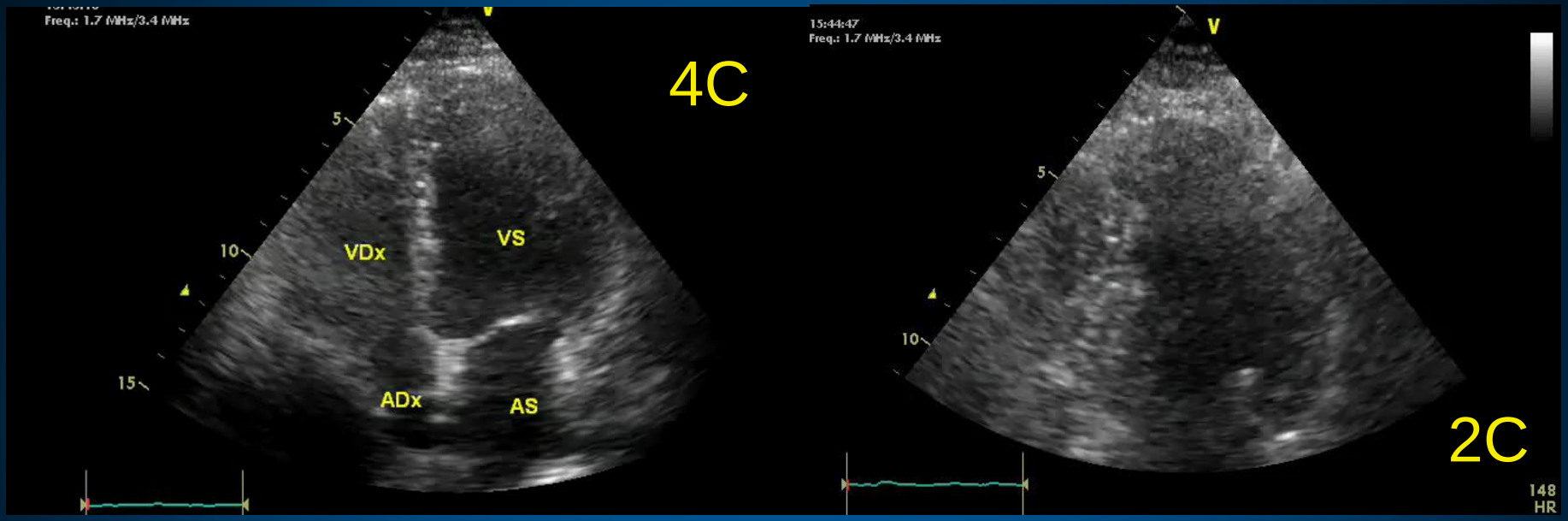
$$\text{WMS Index} = \sum_{n=1}^{n=N} \text{WMS} \div N$$

Global Wall Motion Score (WMS) = 16

Normal Score for ASE 16-segment model

Normal WMS Index = 1

2D BIPLANO: SIMPSON RULE - ∑ DISCHI

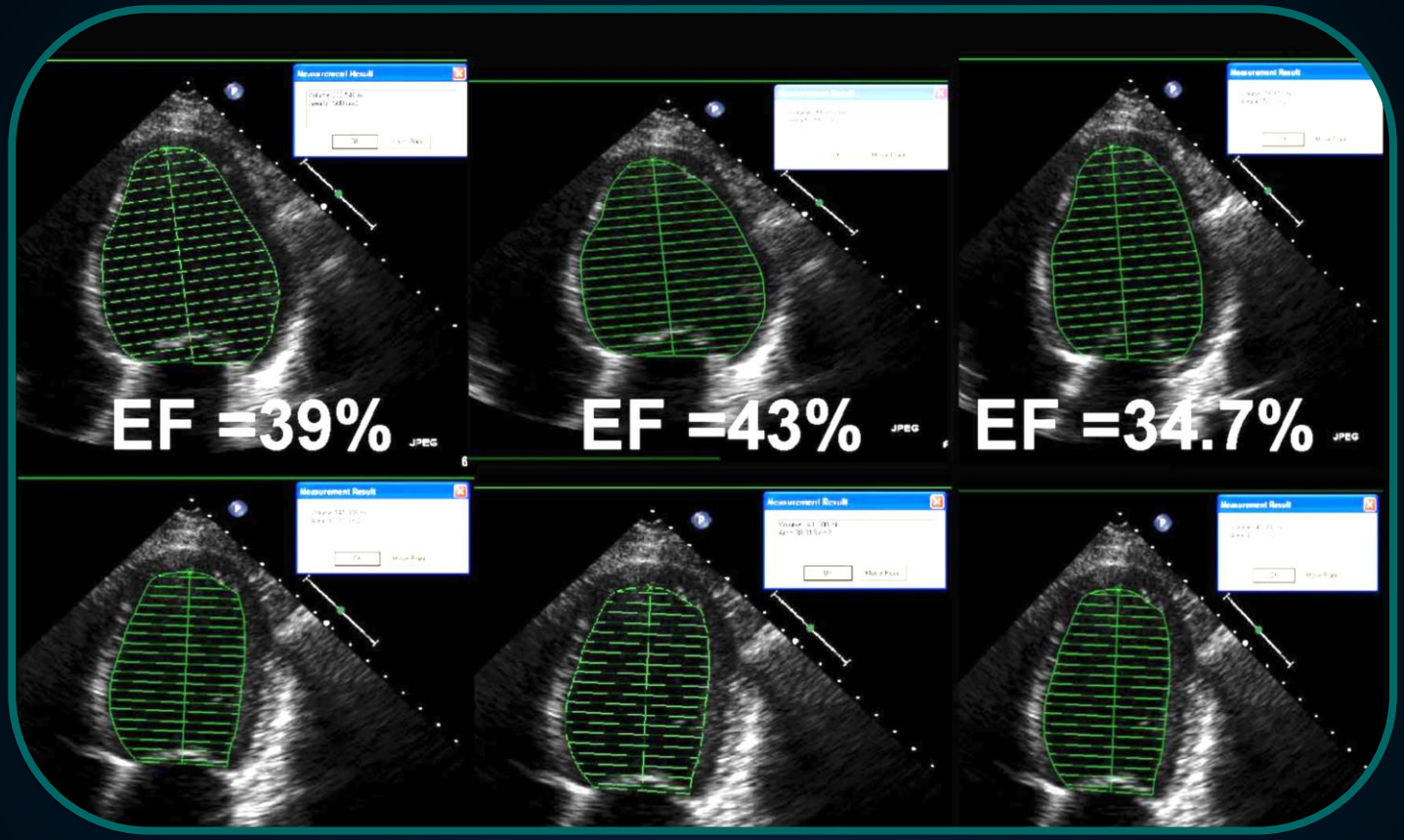


...Ma:

1 mm di differenza nella definizione del bordo endocardico = variazione **10% del volume**

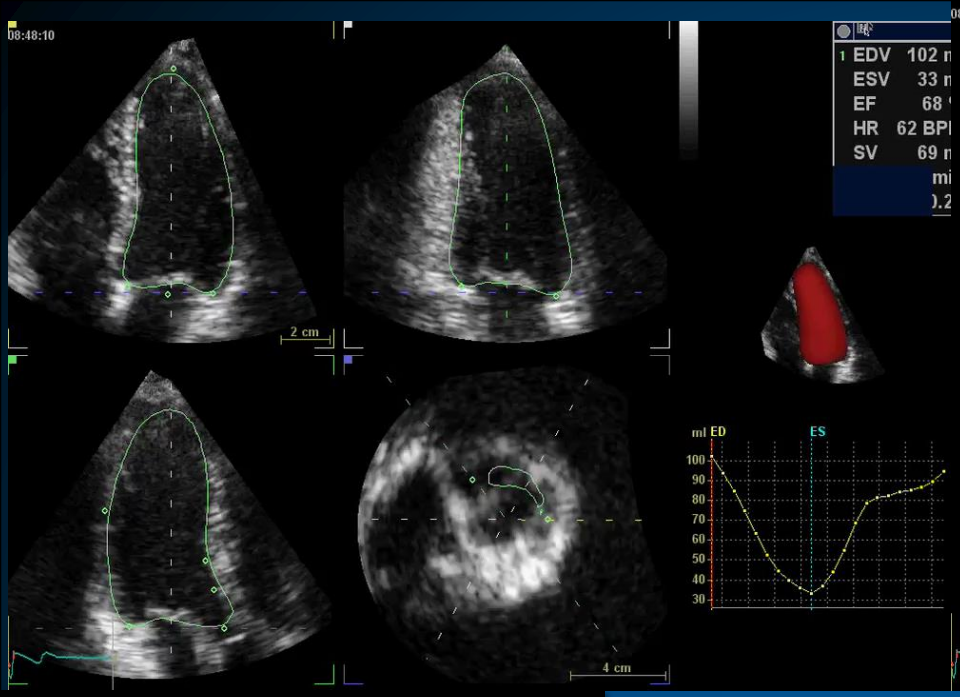
Giorn Ital Card 2009; 10: 516-532

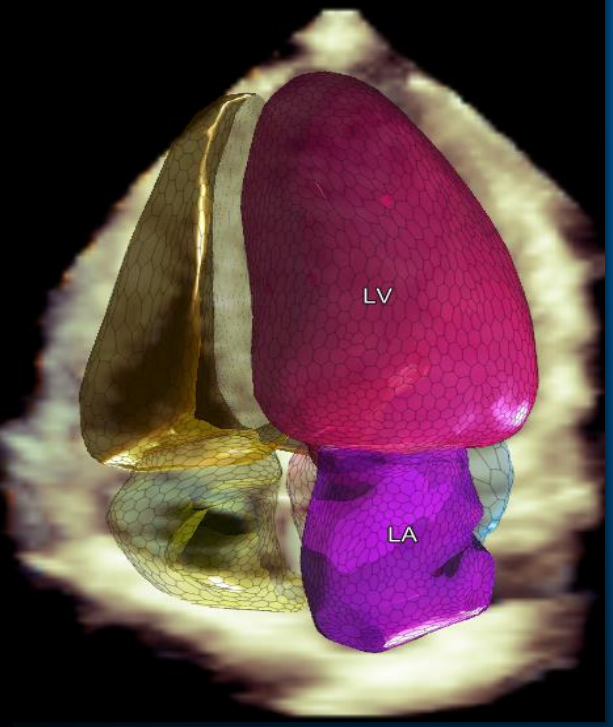
Limitazioni nella valutazione 2D dell'EF



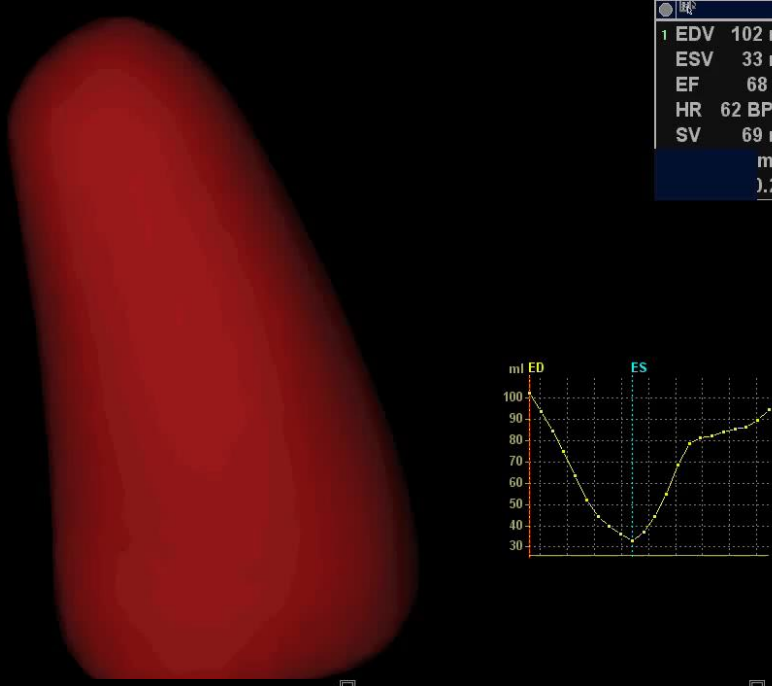
Risk evaluation for decision-making!

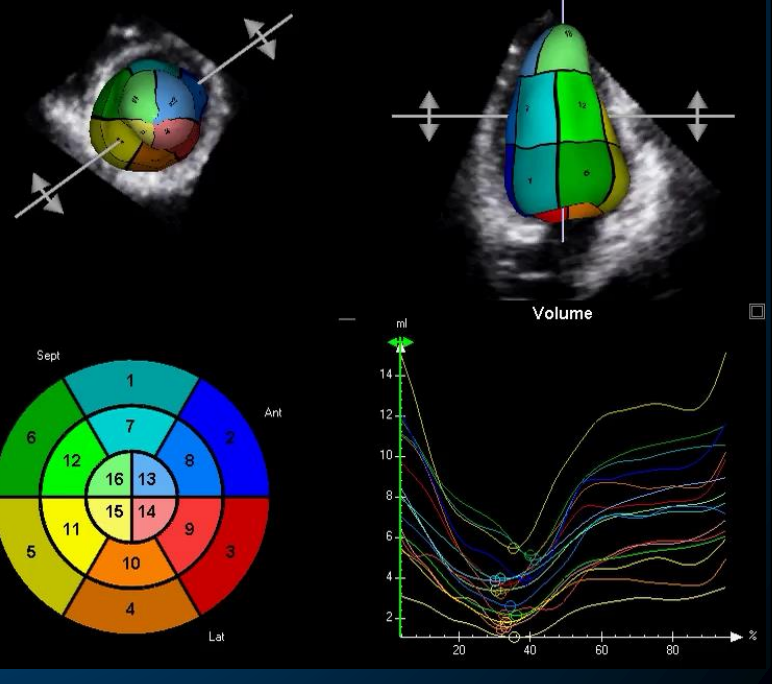
Marwick TH. Heart doi:10.1136/heartjnl-2012-303433


08:48:10
EDV 102 m
ESV 33 m
EF 68
HR 62 BPI
SV 69 m
2 cm
4 cm
ml ED ES
100
90
80
70
60
50
40
30


LV
LA

3D

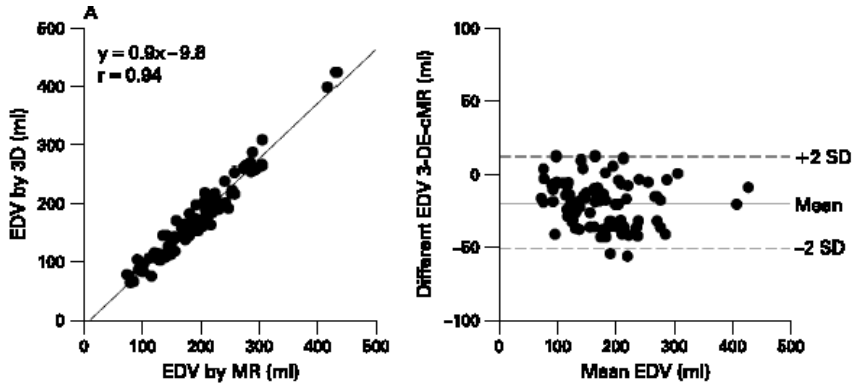

EDV 102
ESV 33
EF 68
HR 62 BP
SV 69
ml ED ES
100
90
80
70
60
50
40
30


Volume
Sept
Ant
Inf
Lat
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
ml
14
12
10
8
6
4
2
20
40
60
80
%

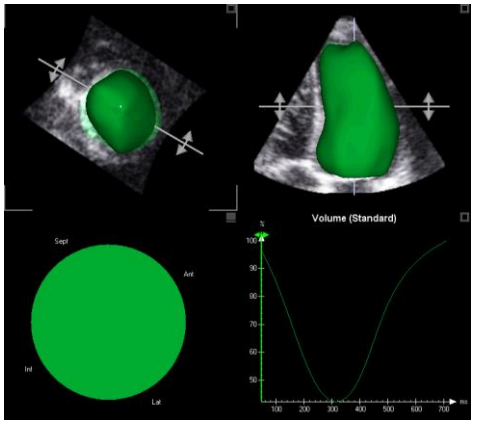
3D echocardiography for evaluating the left ventricle: key points

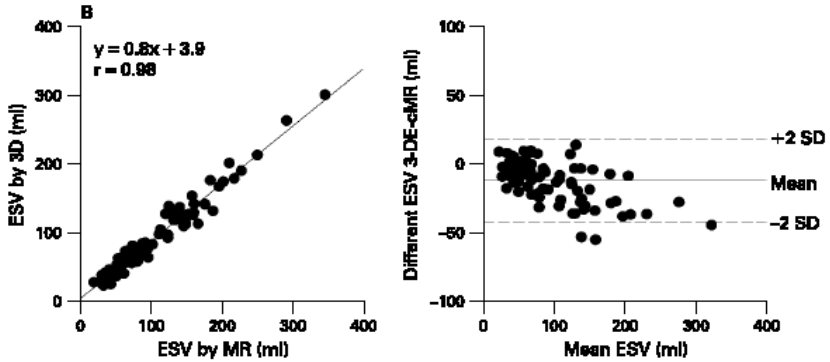
- Left ventricular (LV) morphology and function most common echocardiography request
- M mode and 2D echocardiography make incorrect geometric assumptions about the LV
- Inaccurate and poor reproducibility of M mode/2D analysis
- 3D echocardiography makes no geometric assumptions
- 3D sees the LV "as it is"
- 3D measures endocardial position at >700 points
- 3D echocardiography has excellent correlation with cardiac magnetic resonance (CMR) for volume, mass, and ejection fraction
- 3D reproducibility comparable with CMR

Eco 3D vs MRI in Pts con/senza anomalie del wall motion: Volumi e Frazione di Eiezione

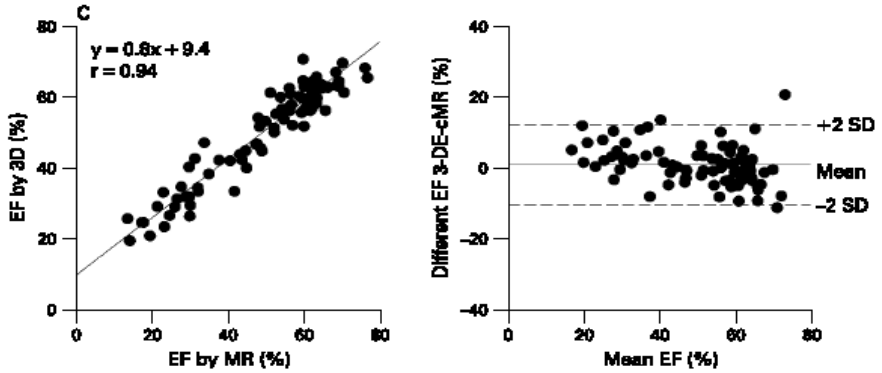


-20 ± 31





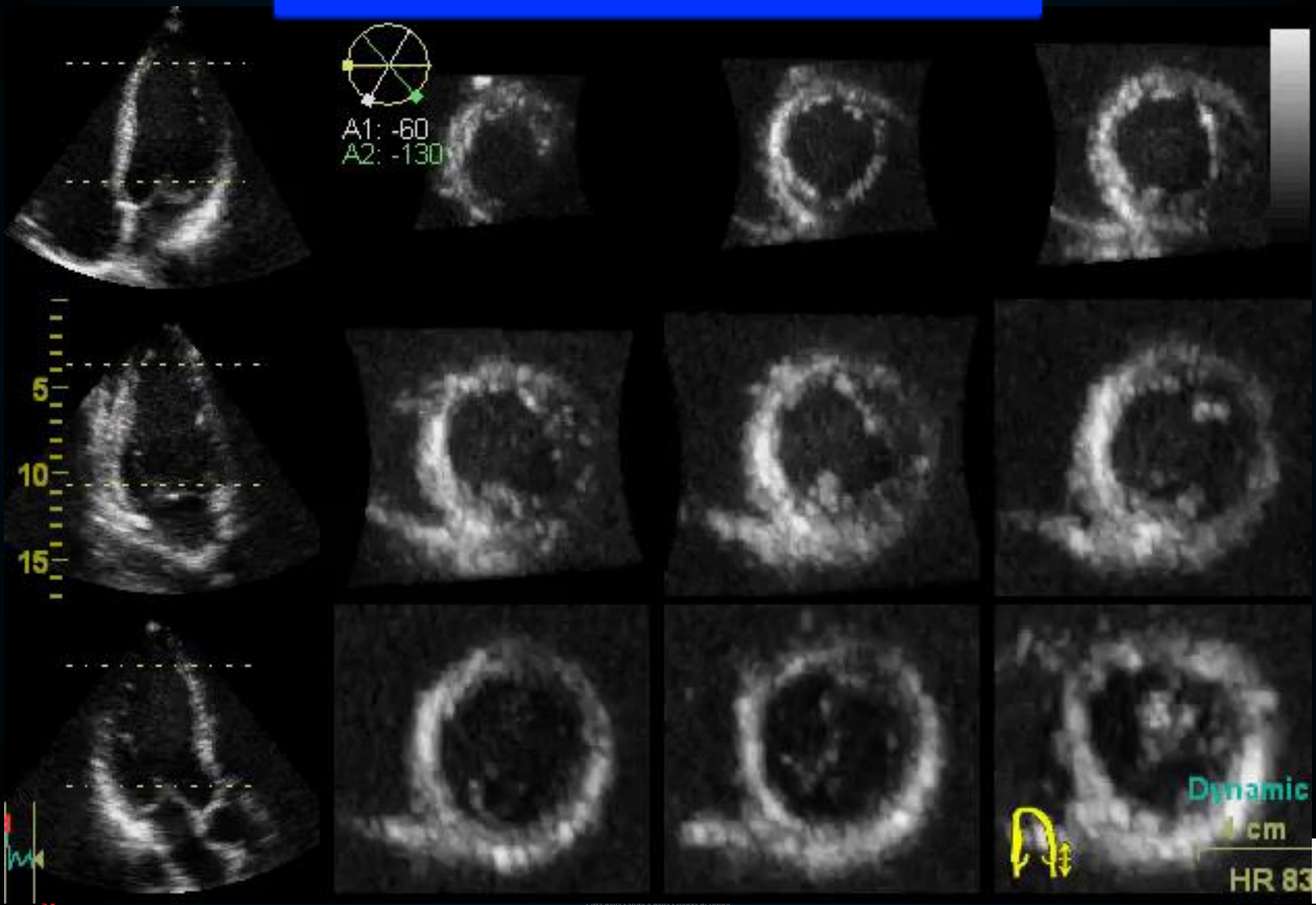
-12 ± 21



5 ± 10

Pouleur AC et al, Heart 2008;94:1050-1057

DYNAMIC 12 SLICES



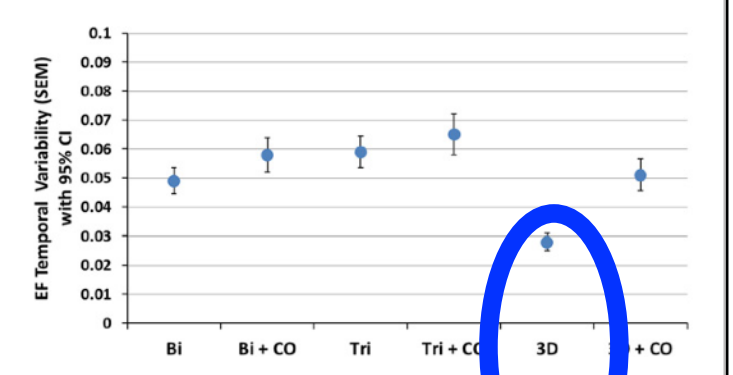


Figure 3 Temporal Variability in EF

Accurate calculation of LVEF should be done with the **best method available** in the echo laboratory (ideally **3DE**)

Conc … ar of follow-up. (J Am Coll Cardiol 2013;61:77–84) © 2013 by the American College of Cardiology Foundation

Table 2 Interobserver and Intraobserver Variability and Minimal Detectable Change for EF Measurements by All 6 Techniques

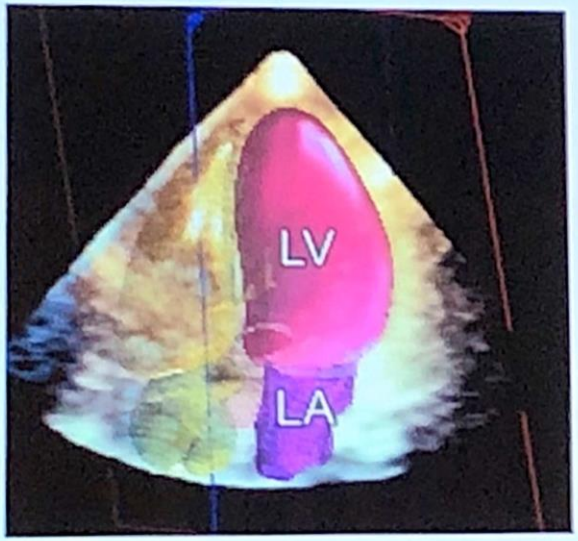
	Bi	Bi + Co	Tri	Tri + Co	3D	3D + Co
Intraobserver	0.033*	0.035*	0.038*	0.037*	0.017	0.026
Min Δ detectable	0.090	0.098	0.104	0.102	0.048	0.072
Interobserver	0.040	0.051*	0.049*	0.048*	0.027	0.038
Min Δ detectable	0.111	0.142	0.135	0.133	0.075	0.100
Interobserver test-retest	0.047*	0.055*	0.058*	0.069*	0.022	0.042*
Min Δ detectable	0.013	0.152	0.162	0.192	0.060	0.115

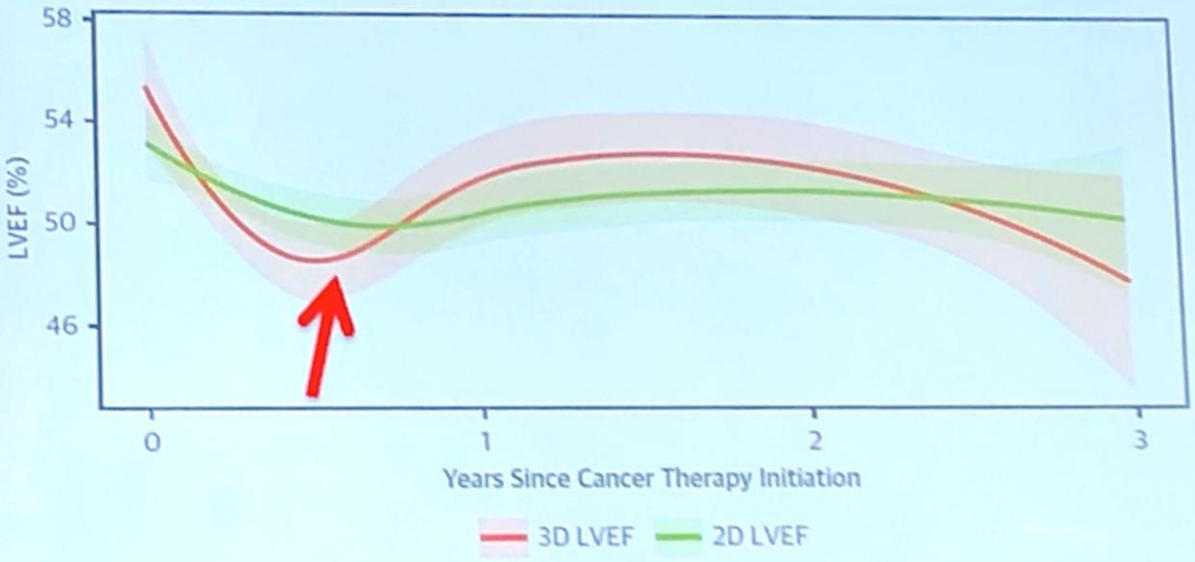
Noncontrast 3D had the lowest intraobserver and interobserver test-retest observer variability and the smallest minimal detectable change. An ejection fraction (… of .033 corresponds to 3.3%. *p < 0.01 *t* test compared with noncontrast 3D.

Bi = biplane Simpson's; BP + Co = biplane Simpson's with contrast; Tri = triplane; Tri + Co = triplane + contrast; 3D = 3-dimensional; 3D + Co = 3-dimensional with contrast.

3DEF BEST TOOL

3DEF changes precedes 2DEF





JACC Cardiovasc Imaging 2018;11(8):1059-6

EF e PITFALLS

- Ogni Pt è caratterizzato da condizioni funzionali ed emodinamiche diverse
- L'EF non riflette accuratamente lo stato contrattile del miocardio, essendo influenzata dalle **condizioni di carico** (→ annotare FC e PAO durante gli esami!)
- **L'EF non sempre riflette la portata cardiaca**, che può:
  - essere conservata in Pts con bassa EF, ma VS di volumetria aumentata
  - essere ridotta in Pts con EF normale, ma piccola volumetria ventricolare / ipertrofia o insufficienza mitralica severa o compromissione della funzione diastolica

VALUTAZIONE DELL'EF: LIMITI

- ↓ EF = perdita di cardiomiociti (danno irreversibile!)
- EF normale anche con alterazioni cinesi segmentaria
- **Indice tardivo, poco sensibile e poco specifico, con bassa accuratezza diagnostica e scarso potere predittivo**

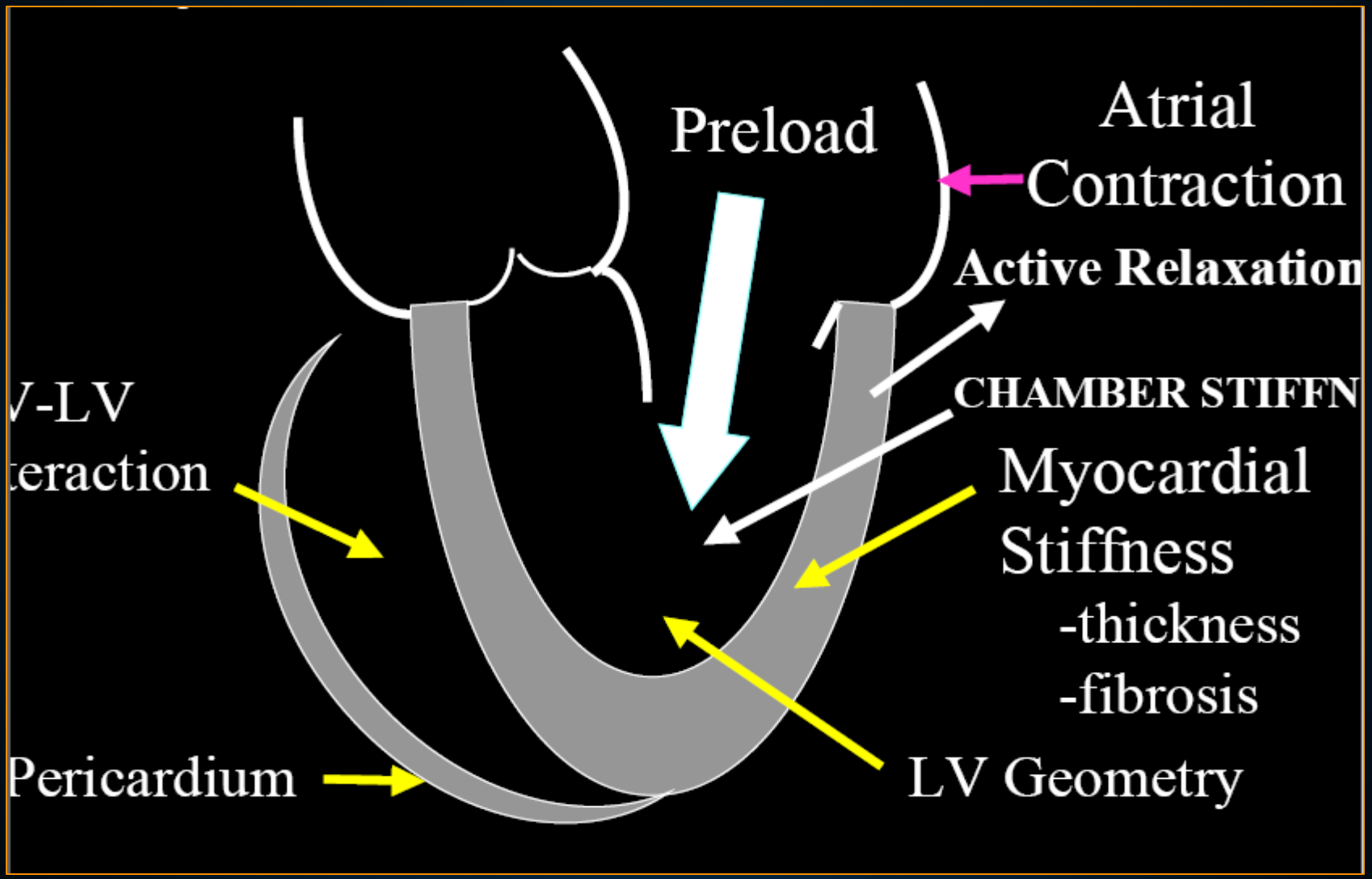
OBIETTIVO DEL CARDIONCOLOGO:

identificazione precoce dei Pts a rischio di sviluppare una disfunzione VS → personalizzazione del programma terapeutico CT e cardioprotezione

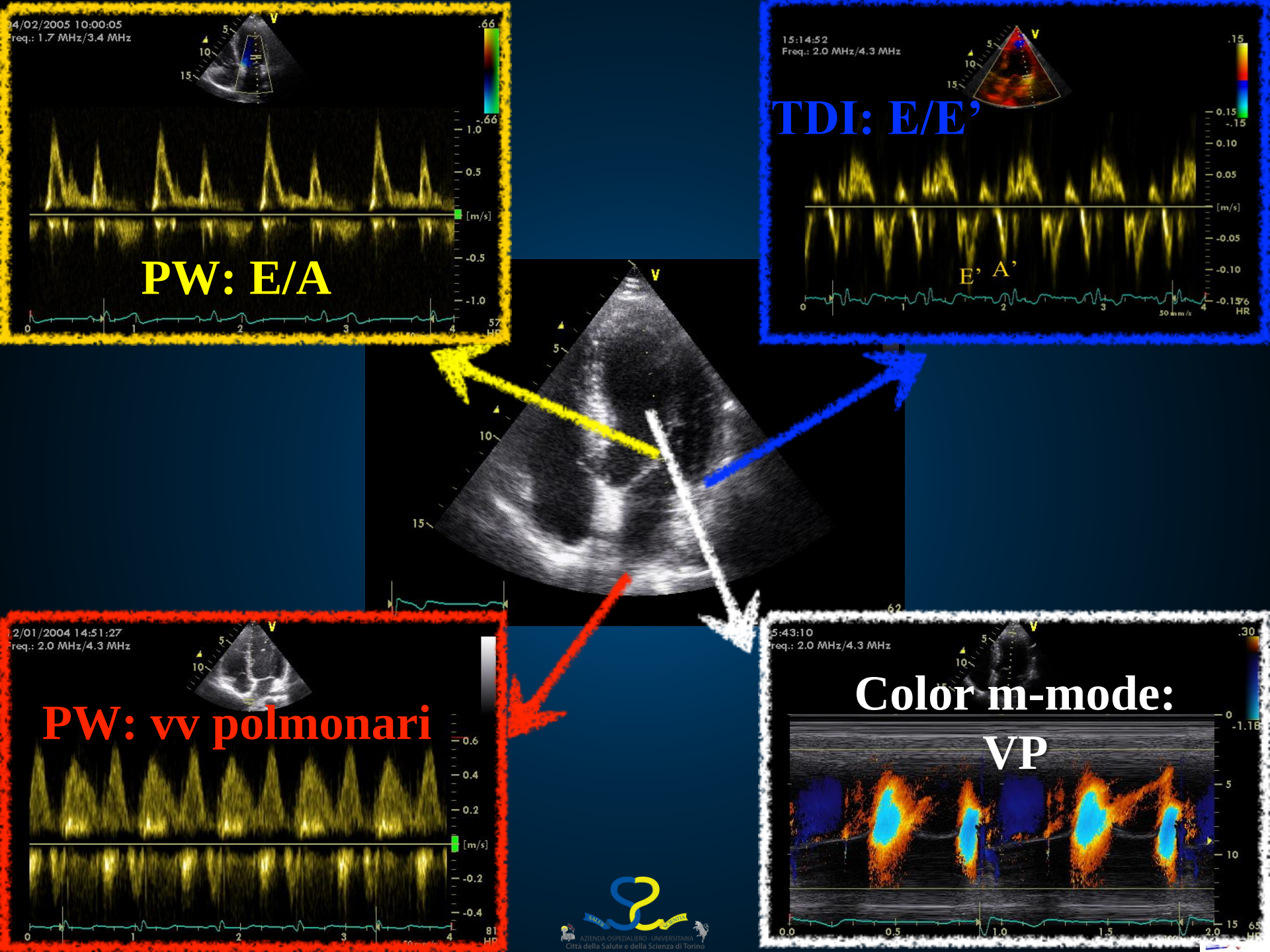
(= identificazione del danno in fase pre-clinica)

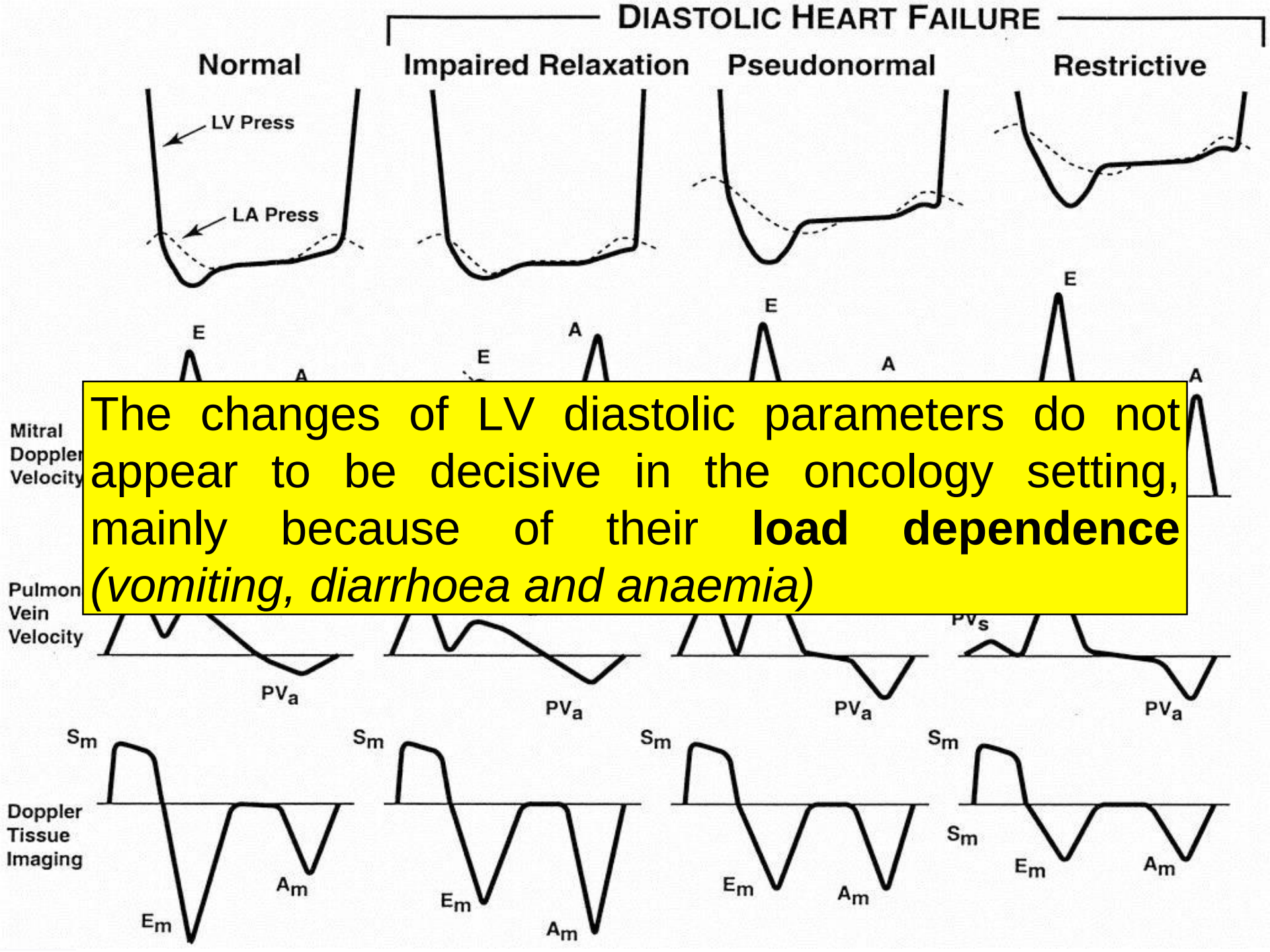
Esistono altre tecnologie echo per evidenziare una CTX prima della riduzione di EF?

DIASTOLIC FUNCTION



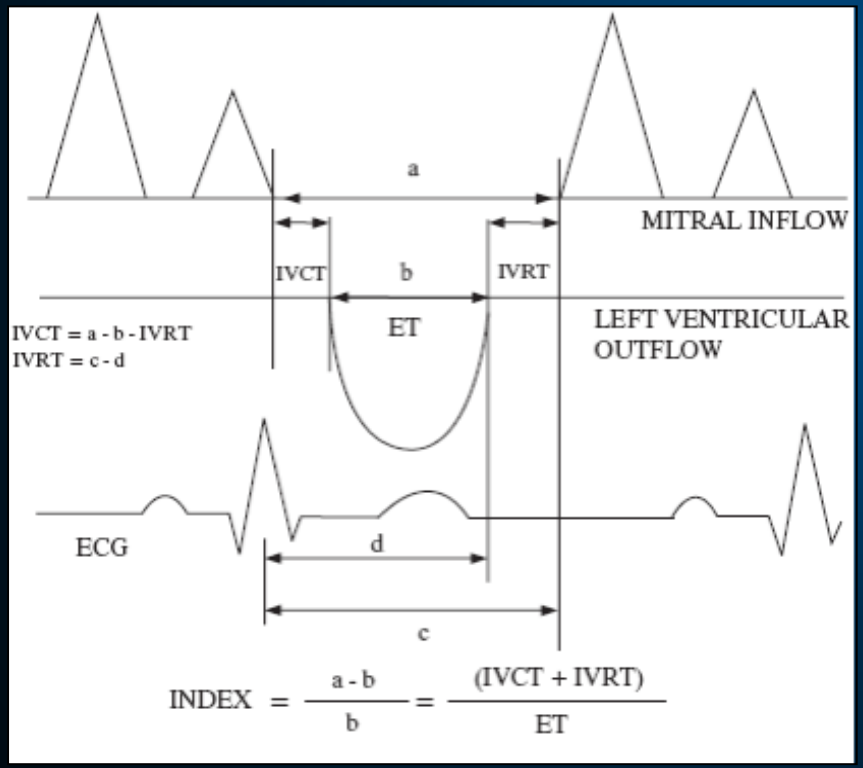
Quinones ASE Review 2007

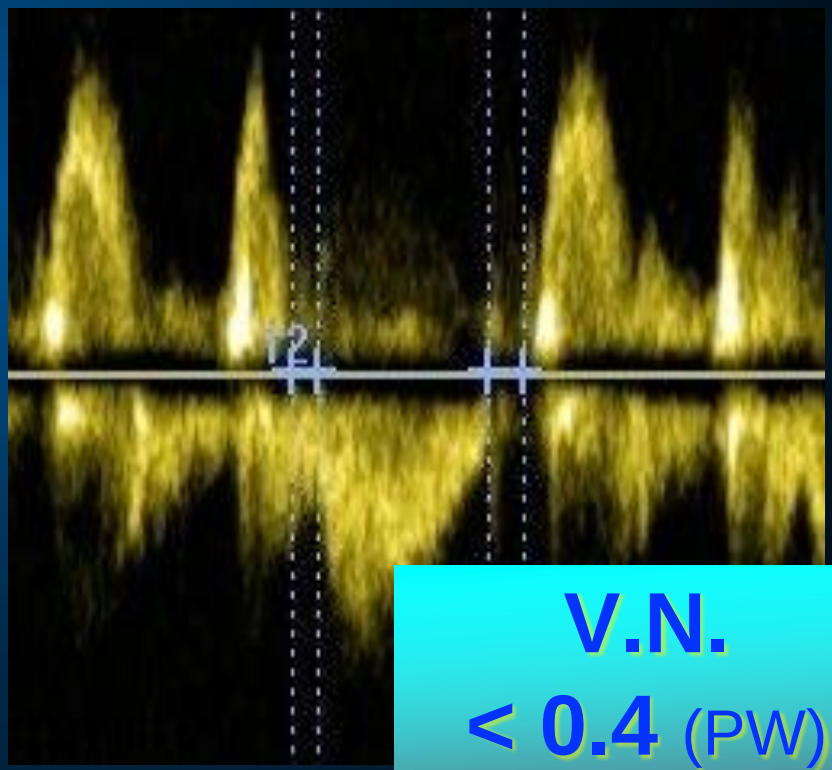

PW: E/A
TDI: E/E’
E’ A’
PW: vv polmonari
Color m-mode:
VP


DIASTOLIC HEART FAILURE
Normal
Impaired Relaxation
Pseudonormal
Restrictive
LV Press
LA Press
Mitral Doppler Velocity
E
A
Pulmon Vein Velocity
PVa
PVs
Doppler Tissue Imaging
Sm
Em
Am
The changes of LV diastolic parameters do not appear to be decisive in the oncology setting, mainly because of their **load dependence** *(vomiting, diarrhoea and anaemia)*

Index of Myocardial Performance (IMP)

Valutazione sisto-diastolica: durata del periodo di contrazione isovolumetrica (IVCT) e di rilasciamento isovolumetrico (IVRT) su eiezione ao (ET) = *TEI Index*



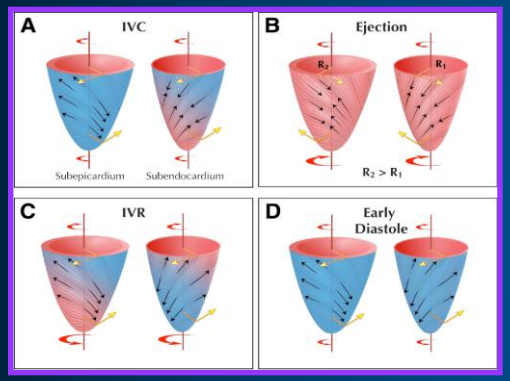


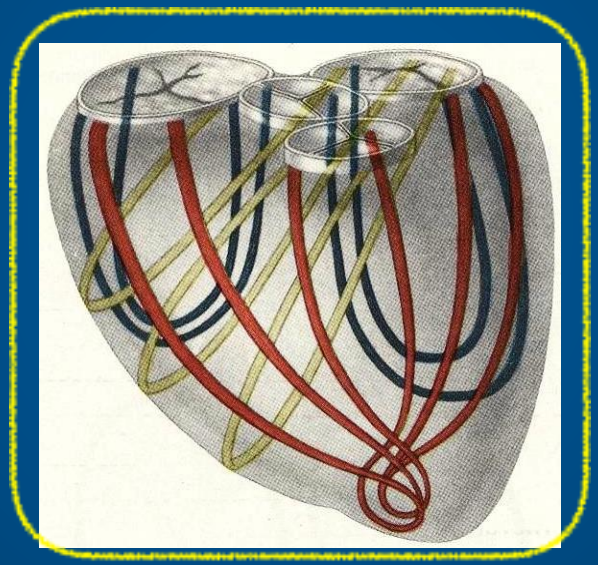
V.N.

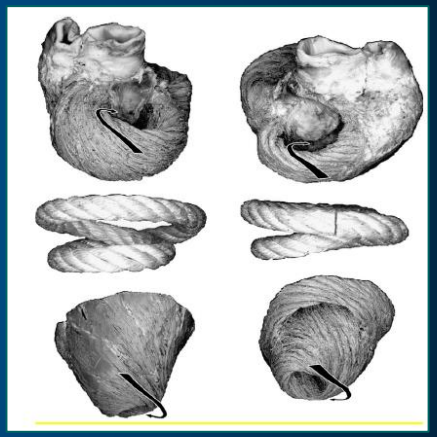
< 0.4 (PW)

< 0.55 *(TDI)*

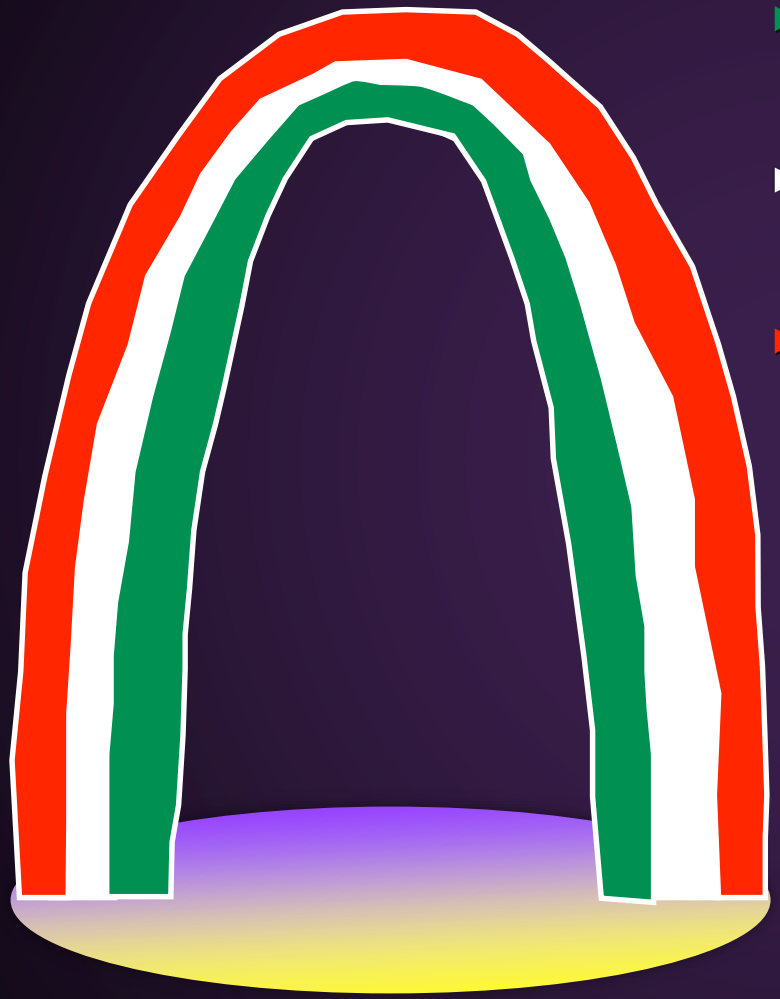
2D-LONGITUDINAL STRAIN







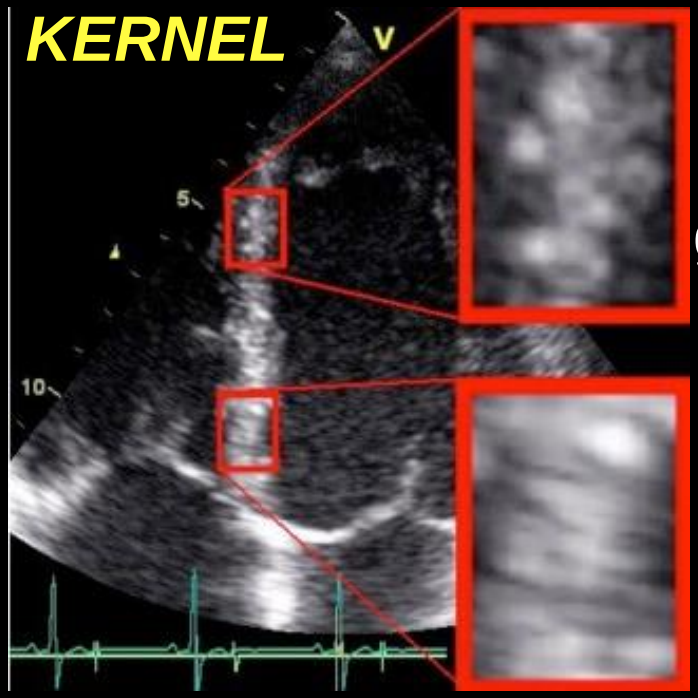
Le FIBRE MIOCARDICHE



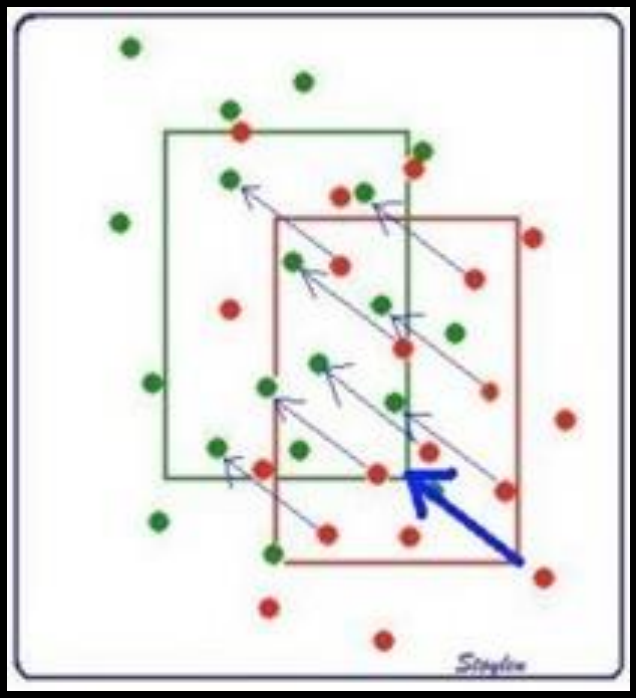
- **Subendocardio: longitudinali**
- **Midwall: circonferenziali**
- **Subepicardio: longitudinali (radiali)**

L'EF valuta solo l'accorciamento radiale, ma l'accorciamento longitudinale contribuisce al 60% della contrazione !

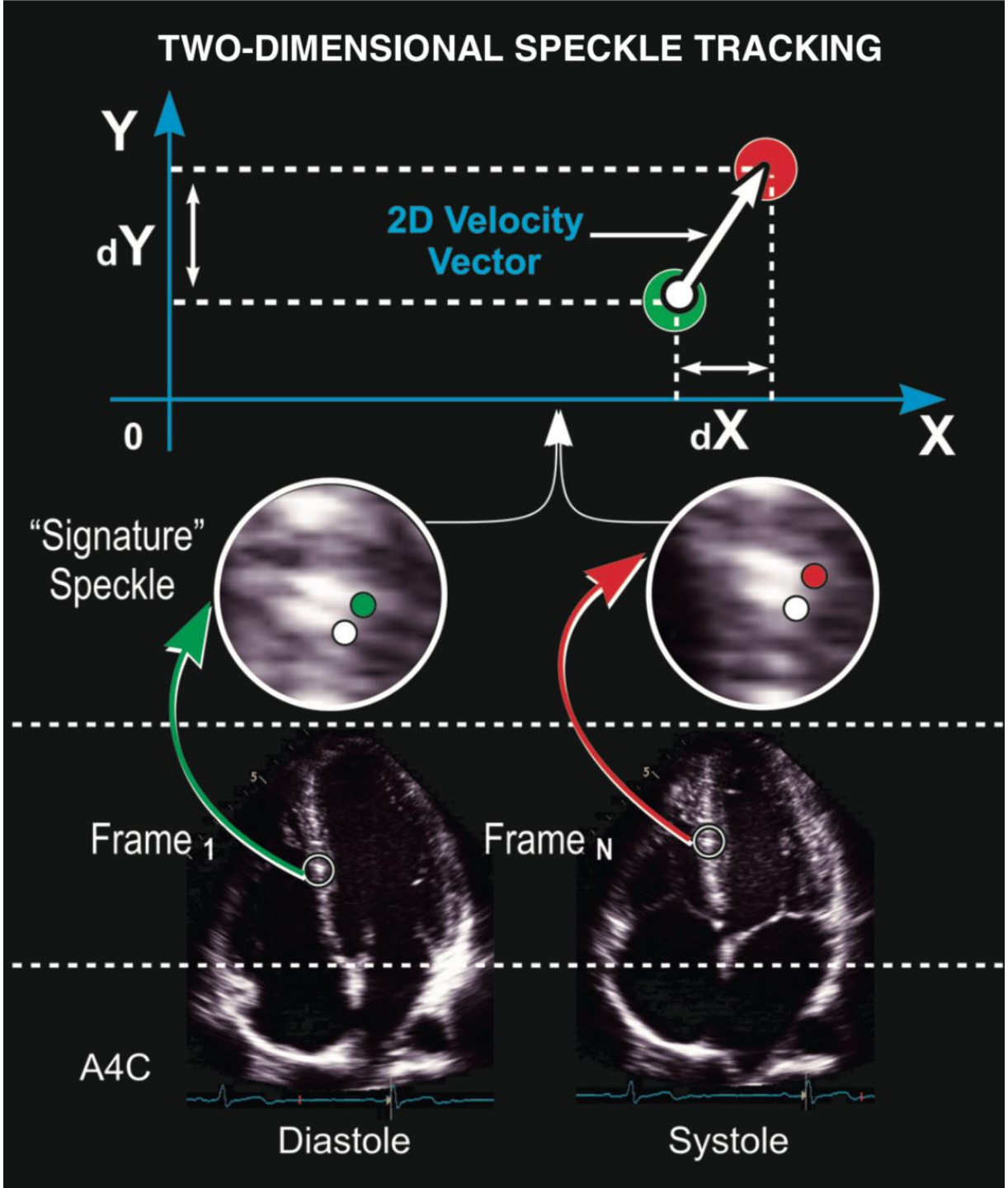
SPECKLE TRACKING



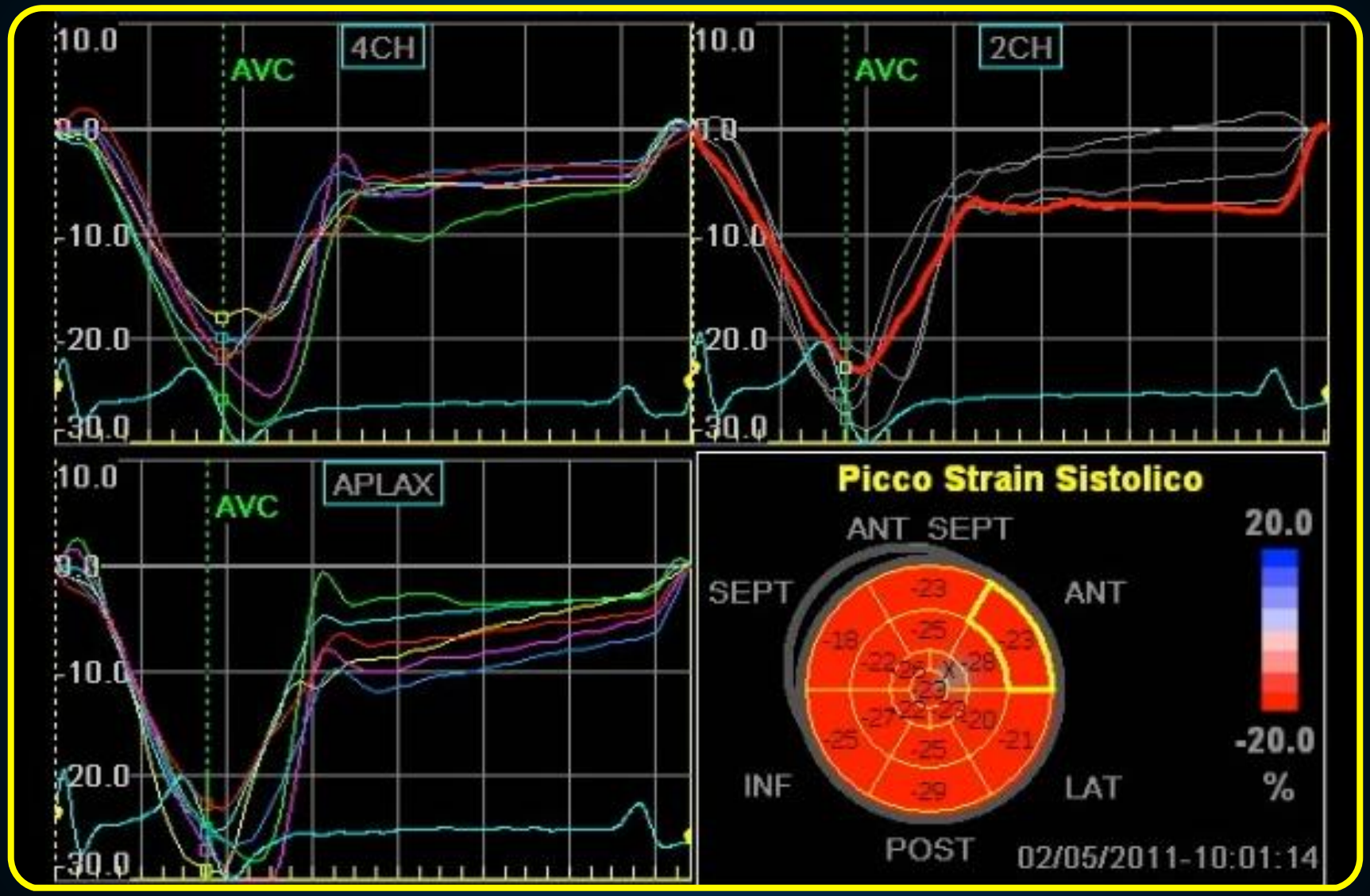
Lo **speckle** è una nuova metodica in grado di valutare lo strain tramite un'acquisizione standard 2D, **indipendente dall'angolo Doppler**



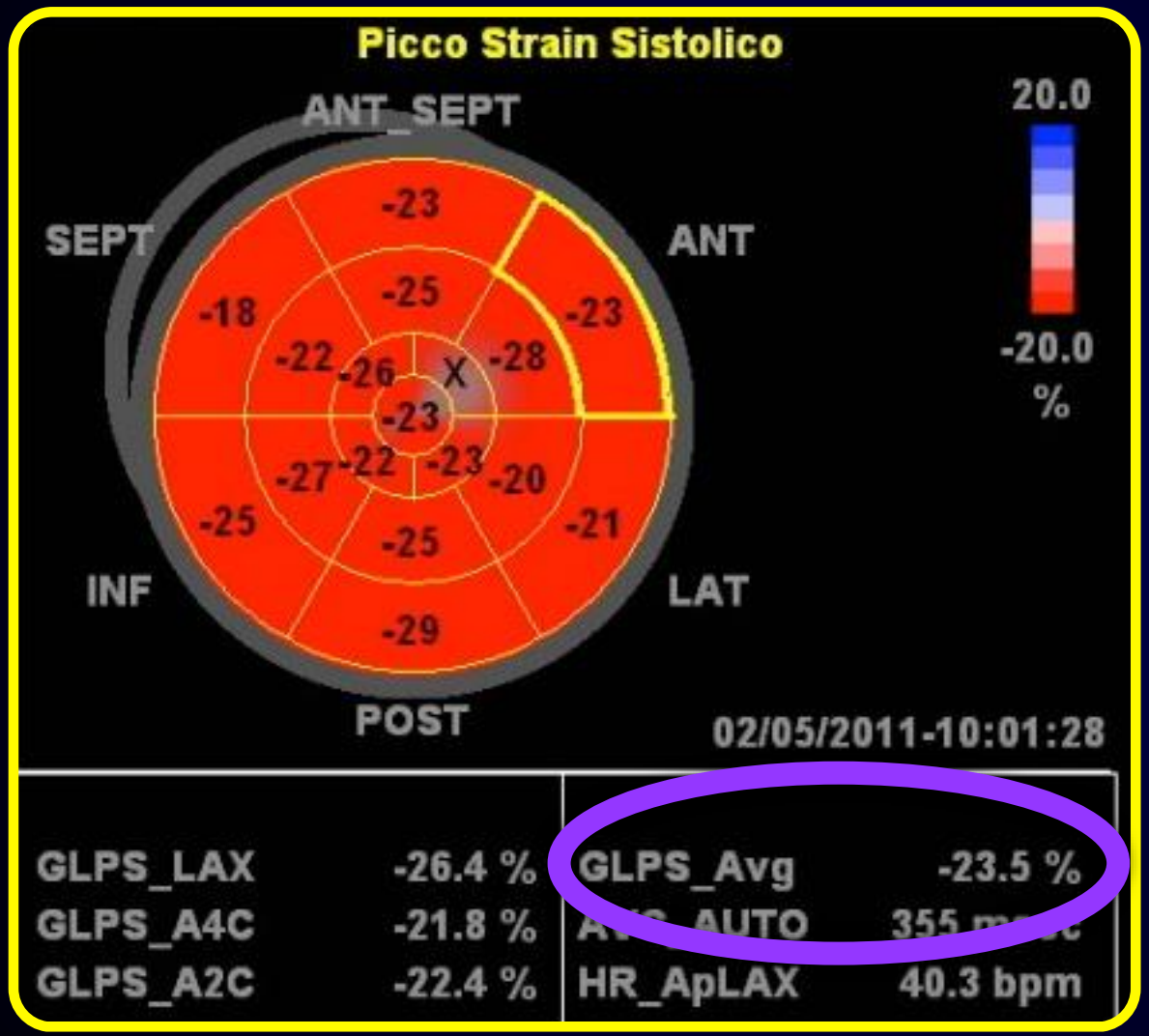
- The random distribution of the speckles ensures that each region of the myocardium has an unique pattern, a **fingerprint**.
- The speckles follow the motion of the myocardium so when the myocardium moves from one frame to the next, the position of this fingerprint will shift slightly, remaining fairly **constant**.
- Thus, if a region (***kernel***) is defined in one frame, a search algorithm will be able to recognise the lie sized and shaped area with the most similar speckle pattern in the next frame, within a defined search area and hence, to find the new position of the kernel


TWO-DIMENSIONAL SPECKLE TRACKING
Y
dY
2D Velocity Vector
0
dX
X
"Signature" Speckle
Frame 1
Frame N
A4C
Diastole
Systole

2D STRAIN


10.0
AVC
4CH
-10.0
-20.0
-30.0
10.0
AVC
2CH
-10.0
-20.0
-30.0
10.0
AVC
APLAX
-10.0
-20.0
-30.0
Picco Strain Sistolico
ANT SEPT
SEPT
ANT
INF
LAT
POST
20.0
-20.0
%
02/05/2011-10:01:14

2D STRAIN: BULL'S EYE



GLS

Global Longitudinal Strain avg

V.N. < -18%

2D-STRAIN: INTERVENDOR VARIABILITY

Journal of the American Society of Echocardiography
June 2015

CLINICAL INVESTIGATIONS

LEFT VENTRICULAR STRAIN MECHANICS: REPRODUCIBILITY

Intervendor Variability of Two-Dimensional Strain Using Vendor-Specific and Vendor-Independent Software

Yasufumi Nagata, MD, Masaaki Takeuchi, MD, Kei Mizukoshi, MD, Victor Chien-Chia Wu, MD, Fen-Chiung Lin, MD, Kazuaki Negishi, MD, Satoshi Nakatani, MD, and Yutaka Otsuji, MD, *Kitakyushu and Suita, Japan; Taipei, Taiwan; and Hobart, Australia*

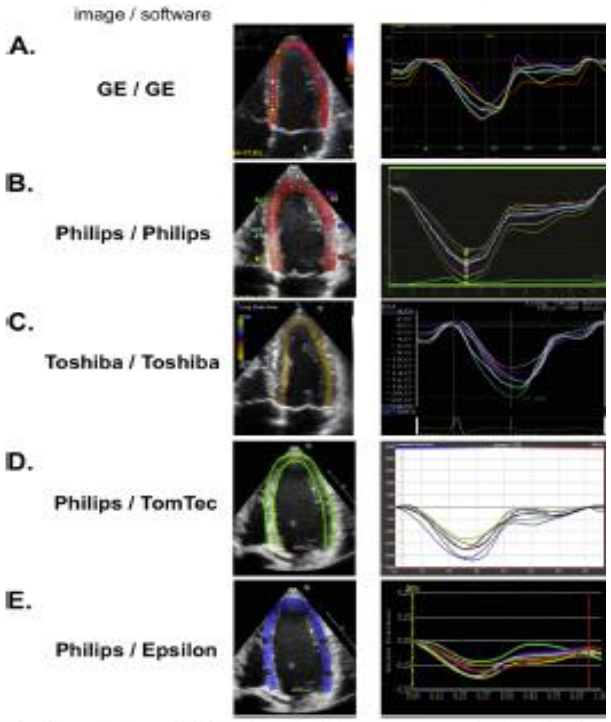


Table 2 Effect of upgrade on GLS for each vendor

	GLS (previous version)	No. of analyzable segments	GLS (current version)	No. of analyzable segments	Bias	*P*	95% LOA	*r*
GE*	19.41 ± 1.62 19.53 ± 1.58	17.4 ± 0.9 17.2 ± 1.1	18.36 ± 1.45 18.43 ± 1.38	17.3 ± 1.1 17.2 ± 1.1	−1.06 −1.10	<.0001 <.0001	−2.37 to 0.25 −2.36 to 0.16	0.91 0.91
Philips†	19.40 ± 1.86 19.40 ± 1.86	16.7 ± 1.8 16.7 ± 1.9	17.09 ± 1.96 17.35 ± 1.95	17.8 ± 0.9 16.7 ± 1.9	−2.31 −2.04	<.0001 <.0001	−5.29 to 0.68 −4.78 to 0.70	0.68 0.73
Toshiba‡	15.75 ± 1.46 15.92 ± 1.37	15.9 ± 1.4 16.0 ± 2.6	16.39 ± 1.52 16.48 ± 1.55	16.5 ± 1.5 16.0 ± 2.6	0.61 0.56	<.0001 <.0001	−1.11 to 2.33 −1.19 to 2.31	0.83 0.82

Table 4 Clinical studies using STE-derived deformation indices during or early after cancer treatment

Study	Echocardiographic method	Cancer type	n	Age, yrs	Female, %	Treatment	Echocardiography timing	Pre-echo	Post-echo	Cardiotoxicity Rate (%)	Thresholds for Toxicity Prediction	Vendor, Reproducibility
Mornos *et al.* (2013)[234]	STE	Breast lymphoma, ALL, AML, osteosarcoma	74 & 37 controls	51 ±11	58	Anthracyclines	Pre, post, and 6, 12, 24 and 52 weeks	GLS -21.2 ± 2.5% GRS 47.8 ± 5.3%	GLS -19.0 ± 2.4% GRS 41.1 ± 5.4% (6 weeks)	13	ΔGLS 2.8% (13.1% relative), sensitivity 79% and specificity 73% at 6 weeks for toxicity at 24 -52 weeks	GE, intraobserver ICC for GLS 0.95, interobserver 0.91
Negishi *et al.* (2013)[155]	STE	Breast	81	50 ± 11	100	Trastuzumab, doxorubicin 46% RT 62%	Pre-trastuzumab, and 6 and 12 months later	GLS -20.7 ± 2.6% GLSR -1.17 ± 0.24/s GLSR-E 1.36 ± 0.28/s	GLS -18.3 ± 2.1% GLSR -1.00 ± 0.15/s GLSR-E 1.20 ± 0.28/s (at 6 months in patients who later had toxicity)	30	GLS change ≥11% between pre-treatment and 6 months, sensitivity 65%, spec 95% or absolute GLS >-20.5 at 6 months, sensitivity 96%, spec 66% for toxicity at 12 months	GE, intraobserver ICC (95% CI) for GLS 0.85 (0.54%-0.96%), GSLR 0.91 (0.70-0.98/s), GLSR-E 0.90 (0.66-0.97/s), Interobserver 0.71 (0.23%-0.92%), 0.85 (0.28-0.97/s), 0.87 (0.56-0.97/s)
Baratta *et al.* (2013)[235]	STE	Breast	36	47 ± 16	58	Doxorubicin 58% trastuzumab 22%	Pre- and 2,3,4, and 6 months after start of therapy	GLS -20.3 ± 2.7% GRS 53.1 ± 4%	GLS -18.9 ± 2.5% (3 months) GRS 50 ± 3.9% (4 months)	19.4	GLS fall ≥ 15% at 3 months, sensitivity 86%, spec 86%. GRS fall ≥ 10% at 4 months, sensitivity 86% spec 69%	GE, mean (SD) absolute difference inter/intraobserver GLS 0.6 (1.4%)/0.2 (1/1%), GRS 3.4 (7.1%)/3.2 (6.6%)
Sawaya *et al.* (2012)[160]	STE	Breast	81	50 ± 10	100	Doxorubicin, epirubicin, trastuzumab, RT 60%	Pre-anthracycline and at 3, 6, 9, 12, and 15 months	GLS -21 ± 2% GRS 53 ± 15% GCS -18 ± 4%	GLS -19 ± 2% GRS 50 ± 17% GCS -16 ± 4% at 3 months	32	Absolute GLS < -19% at 3 months, sensitivity 74%, spec 73% for subsequent toxicity	GE, same variability as in previous study (153)
Sawaya *et al.* (2011)[153]	STE	Breast	43	49 ± 10	100	Doxorubicin, epirubicin, trastuzumab, RT 11.6%	Pre-anthracycline and at 3 and 6 months	GLS -20.5 ± 2.2% GCS 18 ± 4%	GLS -19.3 ± 2.4% GCS 15 ± 4%	21	GLS fall > 10% at 3 months, sensitivity 78%, spec 79% for toxicity at 6 months	GE, intraobserver as absolute mean error (SD) GLS -0.14 (1.1%), interobserver 0.5 (1.5%)
Fallah-Rad *et al.* (2011)[156]	STE	Breast	42	47 ± 9	100	Epirubicin, doxorubicin, trastuzumab, RT 98%	Pre-anthracycline, Pre-trastuzumab and at 3, 6, 9, and 12 months	GLS -19.8 ± 1.8% GLS 41.4 ± 15.2%	GLS -16.4 ± 1.1% GRS 34.5 ± 15.2% (3 months into trastuzumab)	24	Absolute GLS fall of 2.0%, sensitivity 79%, spec 82%. Absolute GRS fall of 0.8%, sensitivity 86%, spec 81% for subsequent toxicity	GE, intraobserver as ICC (COV) GLS 0.94 (3.5%), GRS 0.91 (3.2%). Interobserver 0.90 (5.2%), 0.82 (5.4%)
Hare *et al.* (2009)[162]	TDI and STE	Breast	35	51 ± 8	100	Doxorubicin, epirubicin, trastuzumab, RT 77%	Pre- and/or post-anthracycline and at 3-month	STE GLSR -1.30 ± 0.21/s STE RSR 2.02 ± 0.61/s	STE GLSR -1.24 ± 0.18/s (by 3 months) STE RSR 1.75 ± 0.41/s (by	14	A >1 SD drop in GLSR (toxicity at mean follow-up of 22 ± 6 months)	GE, intra/interobserver as ICC for 2D GLS 0.94/0.91, GLSR

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STATE-OF-THE-ART PAPERS

Use of Myocardial Strain Imaging by Echocardiography for the Early Detection of Cardiotoxicity in Patients During and After Cancer Chemotherapy

A Systematic Review

Paaladinesh Thavendiranathan, MD,*† Frédéric Poulin, MD,* Ki-Dong Lim, MD,*

Miglior predittore CTX =

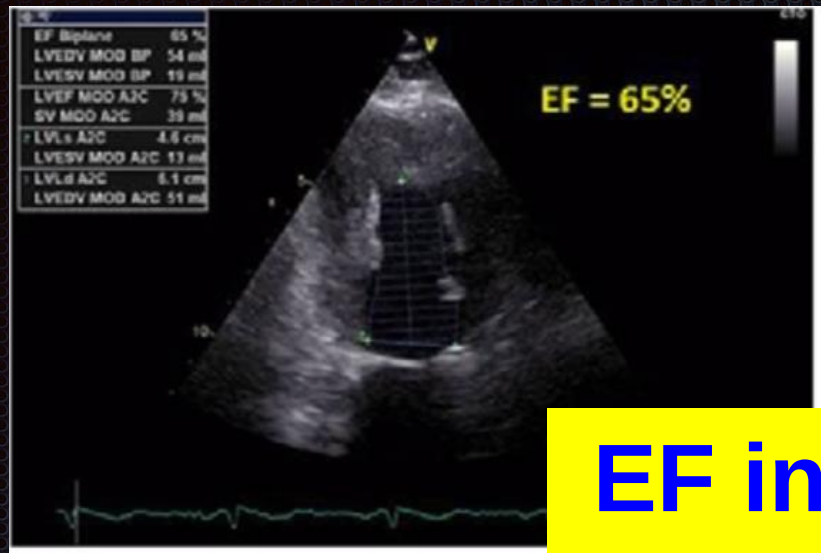
Global Longitudinal Strain S.T.: ↓ 15%

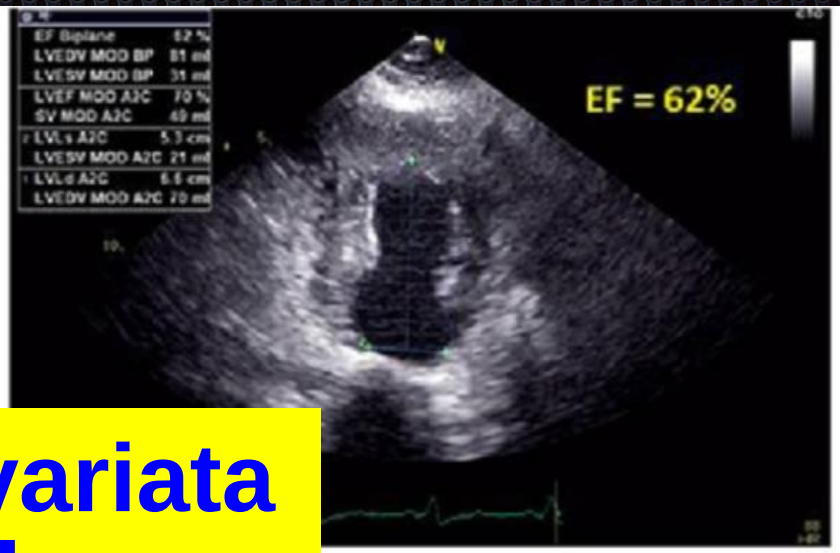
small trials in the research setting. In this systematic review of the current literature, we describe echocardiographic myocardial deformation parameters in 1,504 patients during or after cancer chemotherapy for 3 clinically-relevant scenarios. The systematic review was performed following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines using the EMBASE (1974 to November 2013) and MEDLINE (1946 to November 2013) databases. All studies of early myocardial changes with chemotherapy demonstrate that alterations of myocardial deformation precede significant change in left ventricular ejection fraction (LVEF). Using tissue Doppler-based strain imaging, peak systolic longitudinal strain rate has most consistently detected early myocardial changes during therapy, whereas with speckle tracking echocardiography (STE), peak systolic global longitudinal strain (GLS) appears to be the best measure. A 10% to 15% early reduction in GLS by STE during therapy appears to be the most useful parameter for the prediction of cardiotoxicity, defined as a drop in LVEF or heart failure. In late survivors of cancer, measures of global radial and circumferential strain are consistently abnormal, even in the context of normal LVEF, but their clinical value in predicting subsequent ventricular dysfunction or heart failure has not been explored. Thus, this systematic review confirms the value of echocardiographic myocardial deformation parameters for the early detection of myocardial changes and prediction of cardiotoxicity in patients receiving cancer therapy. (J Am Coll Cardiol 2014;63:2751–68) © 2014 by the American College of Cardiology Foundation

STRAIN

- Myocardial deformation (strain) can be measured using DTI or 2D STE. The latter is favored because of a lack of angle dependency.
- GLS is the optimal parameter of deformation for the early detection of subclinical LV dysfunction.
- Ideally, the measurements during chemotherapy should be compared with the baseline value. In patients with available baseline strain measurements, a relative percentage reduction of GLS of <8% from baseline appears not to be meaningful, and those >15% from baseline are very likely to be abnormal.
- When applying STE for the longitudinal follow-up of patients with cancer, the same vendor-specific ultrasound machine should be used.

EUROPEAN SOCIETY OF CARDIOLOGY®



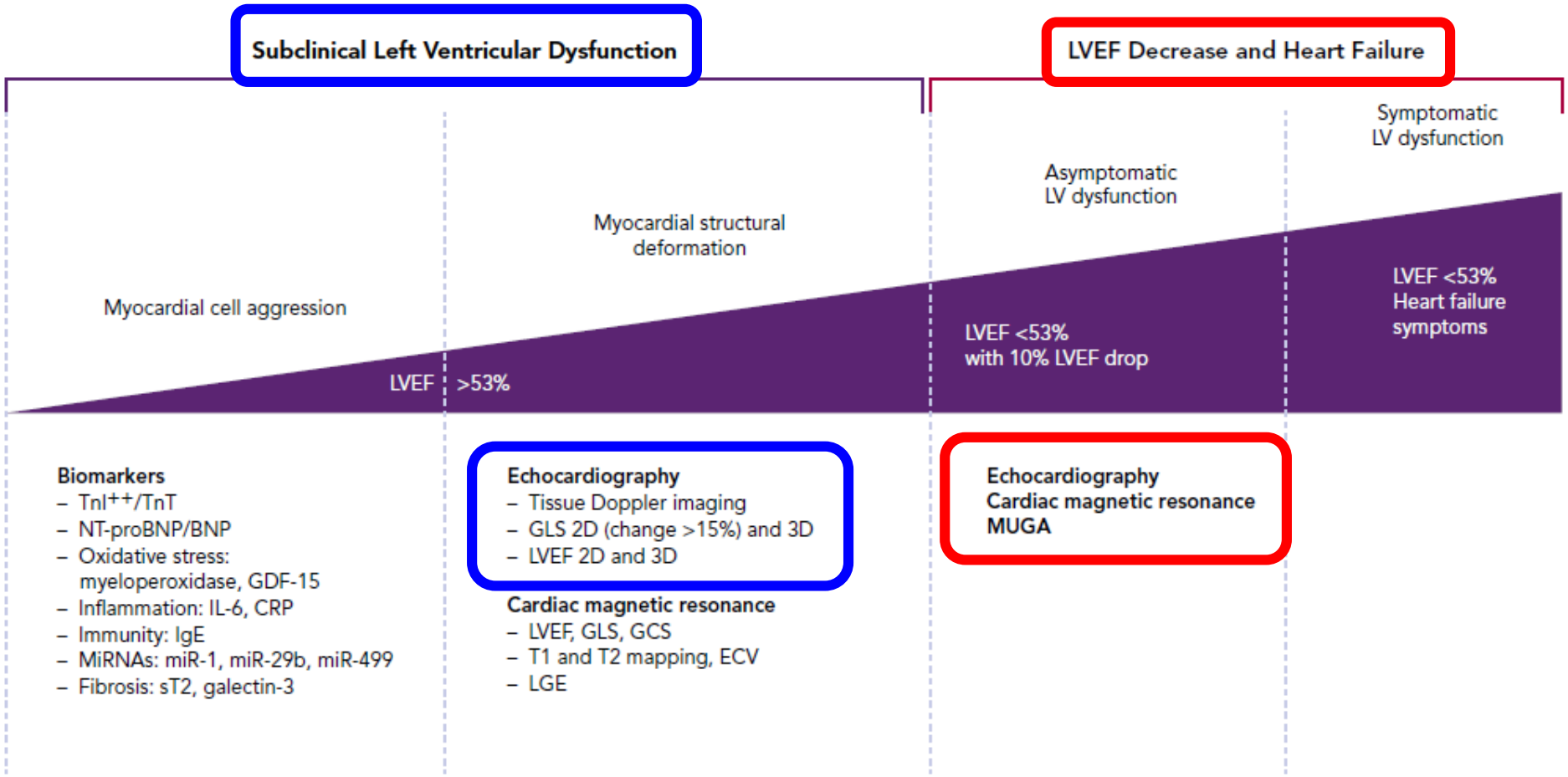


EF invariata
GLS ↓ 16%

At baseline

EC completion

Figure 1: Diagnosing Subclinical Left Ventricular Dysfunction During Chemotherapy Before Heart Failure Occurrence



BNP = brain natriuretic peptide; CRP = C-reactive protein; ECV = extracellular volume; GCS = global circumferential strain; GLS = global longitudinal strain; IgE = immunoglobulin E; IL-6 = interleukin-6; LGE = late gadolinium enhancement; LV = left ventricular; LVEF = left ventricular ejection fraction; MiRNA = microRNA; MUGA = multigated acquisition scan; NT-proBNP = N-terminal pro brain natriuretic peptide; TnI = troponin I; TnT = troponin T.

CORONARY ARTERY DISASE

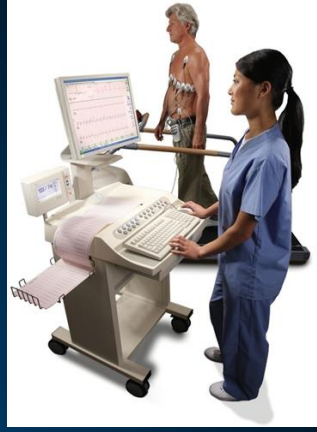
Table 7 **Pathophysiological mechanisms of coronary artery disease in cancer treatment**[7,60,81,99,117–123]

Agent	Pathophysiological mechanism	Risk of coronary artery disease and acute coronary syndrome
Fluoropyrimidines (5-FU, capecitabine, gemcitabine)	• Endothelial injury • Vasospasm	• Up to 18% manifest myocardial ischaemia • Up to 7–10%: silent myocardial ischaemia
Platinum compounds (cisplatin)	• Procoagulant status • Arterial thrombosis	• 20-year absolute risk of up to 8% after testicular cancer • 2% risk of arterial thrombosis
ponatinib	• Procoagulant status • Arterial thrombosis • Endothelial injury	• Risk of arterial thrombosis: bevacizumab 3.8%, sorafenib 1.7%, sunitinib 1.4%
Radiation	• Endothelial injury • Plaque rupture • Thrombosis	• 2–7-fold increased relative risk of myocardial infarction • Cumulative 30-year coronary events incidence of 10% in Hogdkin lymphoma survivors • Risk proportional to irradiation dose

*... typically manifest **10 – 15 years after** the initial treatment, and **younger** patients are more susceptible*

5-FU = 5-fluorouracil; VEGF = vascular endothelial growth factor.

DIAGNOSI di CORONAROPATIA

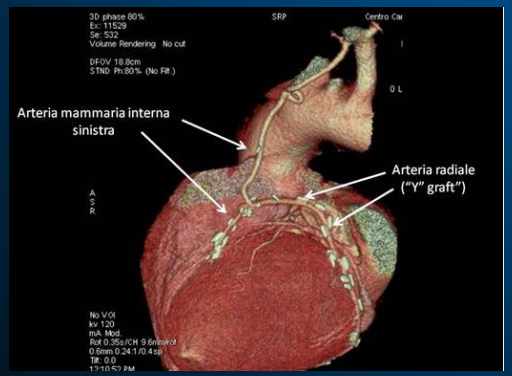


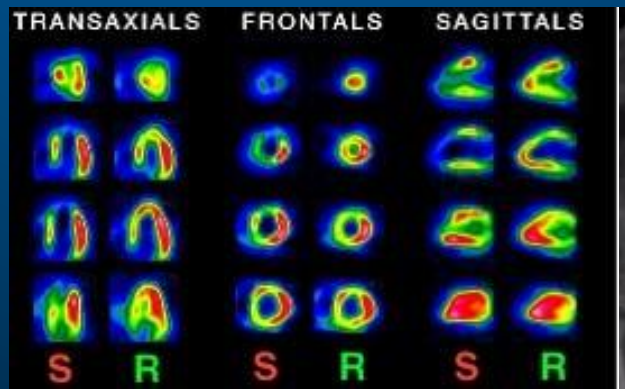
- TEST ERGOMETRICO

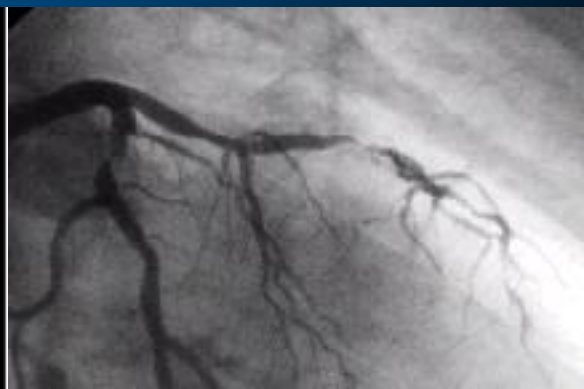
- ECOSTRESS (dpm – dobu – sforzo)
- SCINTIGRAFIA MIOCARDICA (dpm-Tc / sforzo-TI201)

- CORONAROGRAFIA (anche coronarite da RX-terapia)
- TEST ERGONOVINA (spasmo!)

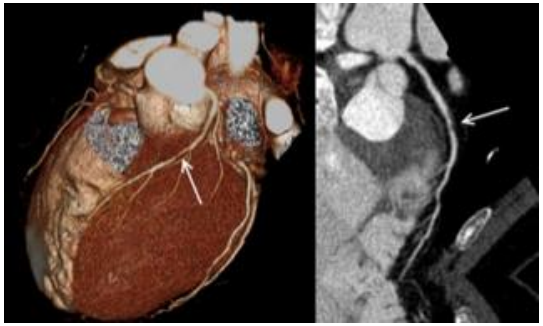
- TC CORONARICA



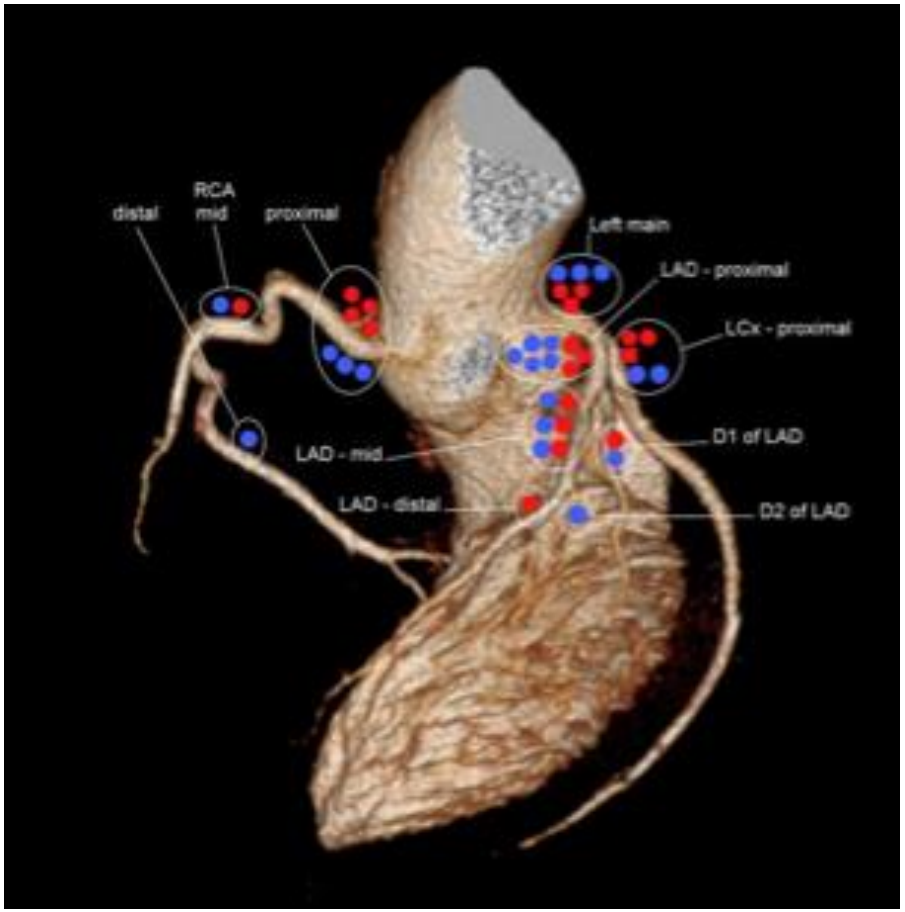




Coronary Artery Disease Detected by Coronary Computed Tomography Angiography in Adult Survivors of Childhood Hodgkin Lymphoma



Location of Plaque	No. (%)
Left main artery	6 (15)
Left anterior descending artery	
Proximal	8 (21)
Middle	6 (15)
Distal	1 (3)
Diagonals	2 (5)
Left circumflex artery	
Proximal	5 (13)
Distal	0 (0)
Right coronary artery	
Proximal	7 (18)
Middle	2 (5)
Distal	2 (5)



***CAD prevalence: 39%** (normal population: 8.5-11%)*

Mulrooney at al, Cancer; 2014

CARDIAC MAGNETIC RISONANCE

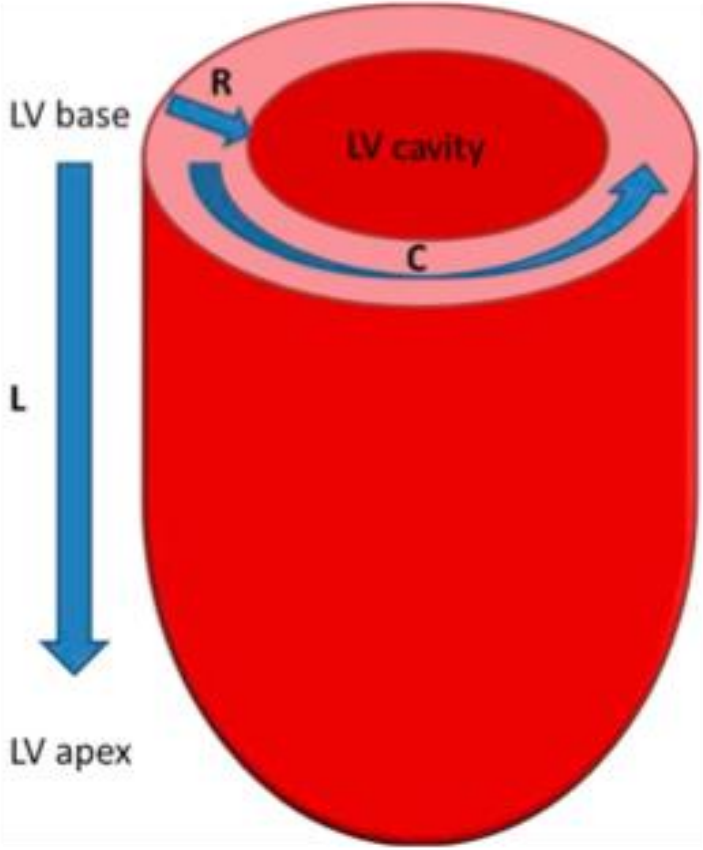
- CMR is **not currently used** as a first-line tool because of its **high cost and limited availability**
- It should be considered in **non-diagnostic echocardiograms** or in **unexplained LV and/or RV enlargement**, or morphological abnormalities consistent with **infiltrative cardiomyopathies**
- **Late gadolinium enhancement (LGE)**: differentiation of **non-ischaemic and ischaemic myocardial fibrosis** or **myocarditis** by immunotherapy
- **T1- and T2-weighted CMR**: **intracellular and interstitial oedema**, alterations which can precede reduction in both LVEF and GLS

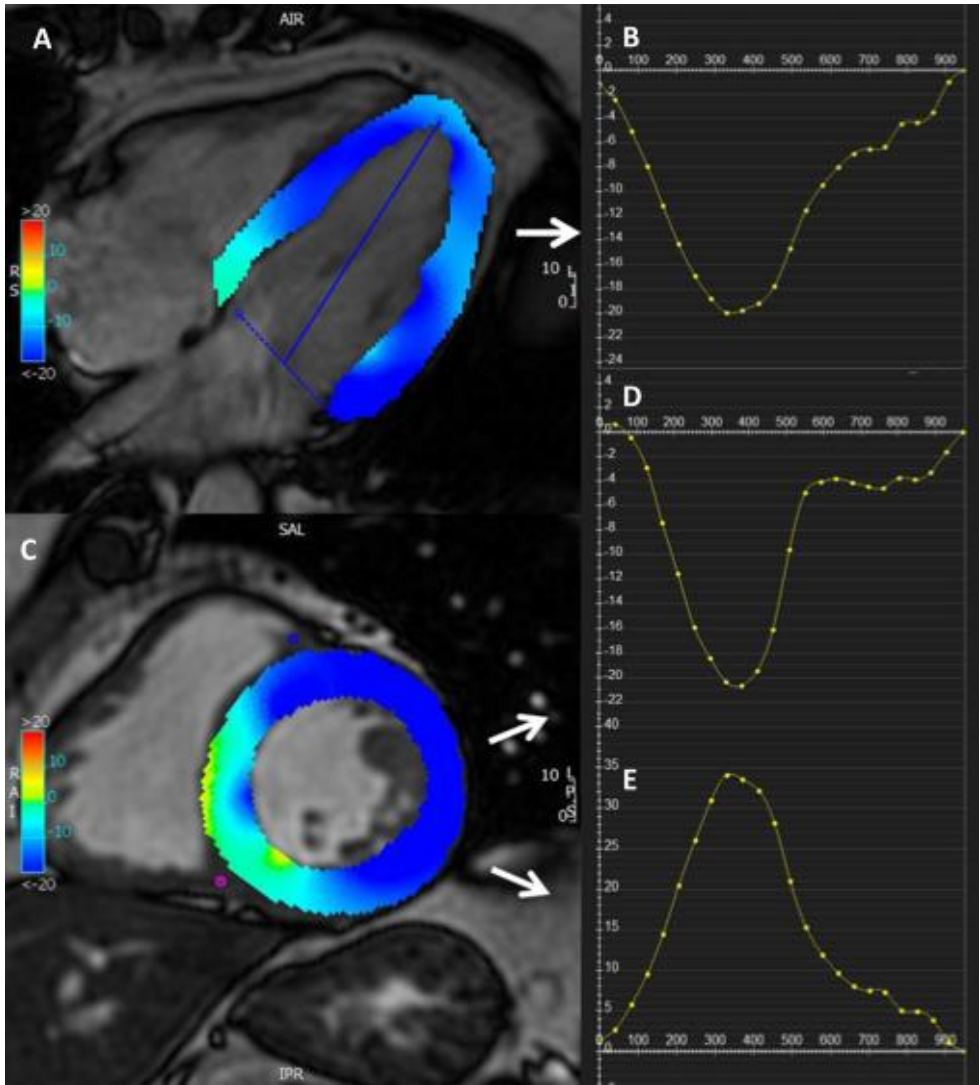
Heart Fail Rev (2017) 22:465–476
DOI 10.1007/s10741-017-9621-8

2017

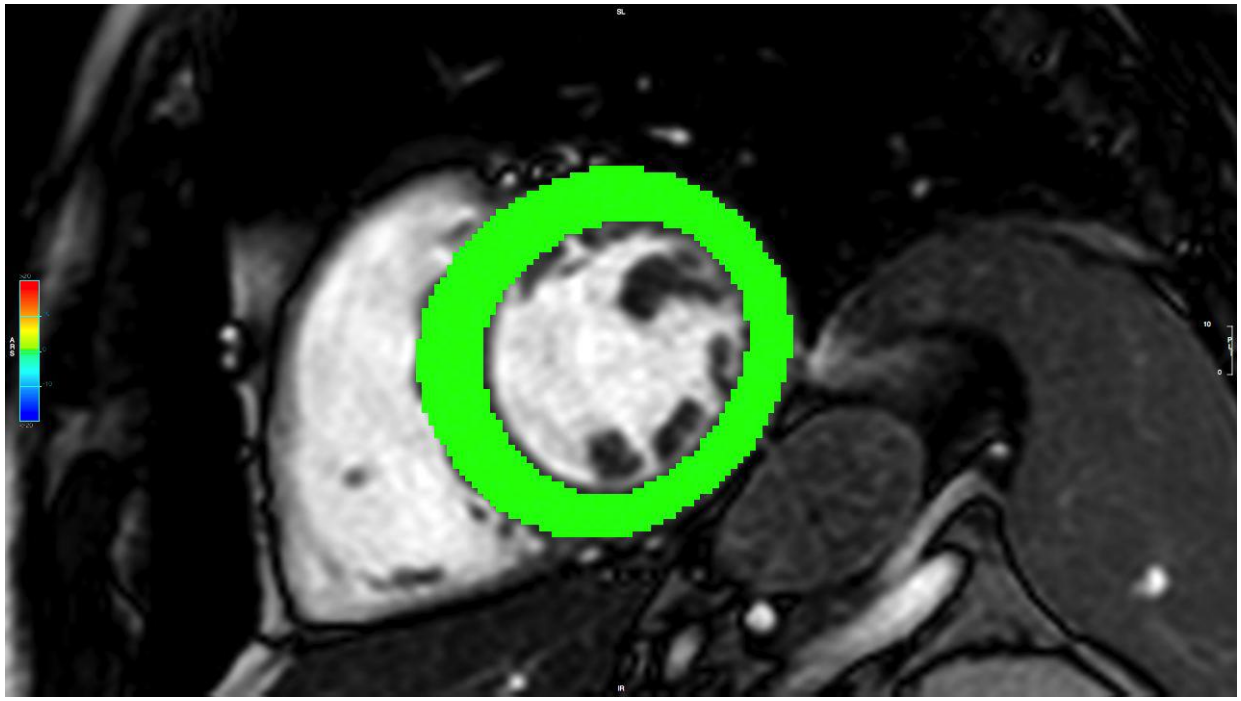
Strain imaging using cardiac magnetic resonance

A. Scatteia[1,2] · A. Baritussio[1] · C. Bucciarelli-Ducci[1]

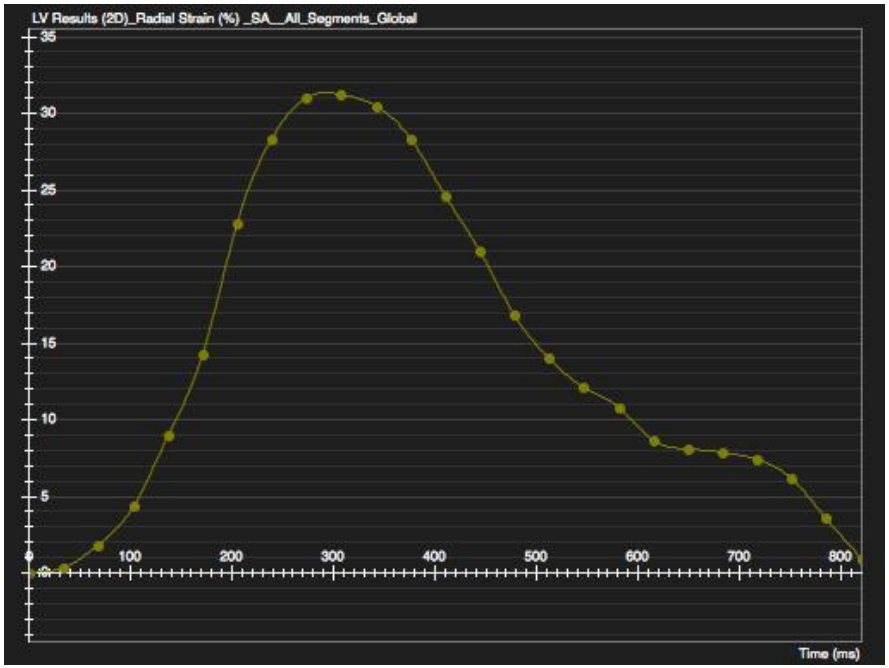




Courtesy by Riccardo FALETTI



Strain CMR



Courtesy by Riccardo FALETTI

Tempistica del follow-up

TIMING e FREQUENZA del FOLLOW-UP

- **TIPO** di trattamento antitumorale
- **ETÀ** di inizio del trattamento antitumorale (***5 aa***)
- **DOSE CUMULATIVA AC** (***300 mg/m²*** doxo-eq.)
- **DOSE RADIANTE TOTALE** (***30 Gy***)
- **PROTOCOLLO E DURATA DI INFUSIONE**
- **RISCHIO CARDIOVASCOLARE BASALE**

Tempistica di sorveglianza

- Assenza di vere guidelines
- Basata su **opinioni di consenso**
- **Primi controlli: 1° anno** da fine terapia
- **Follow-up**:
  - **ogni 5 anni**
  - **ogni 2 anni se: AC > 300 mg/m2 o RT > 30 Gy**
  - **Annuale se:**
    - **AC > 300 mg/m2 + RT > 30 Gy o**
    - **inizio < 5 aa**
- Utile, inoltre, **test di ischemia ogni 10 anni**


That's all Folks!
Any Question ?