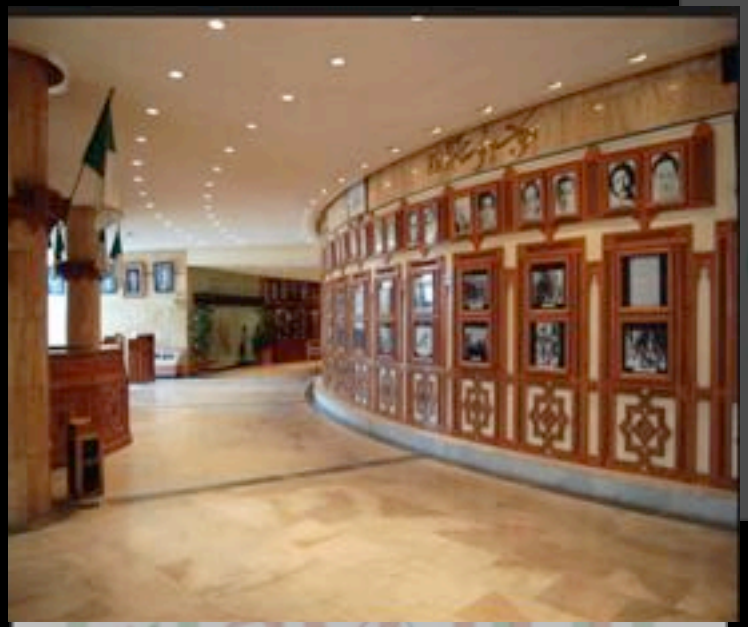










VENTRICULOGRAPHIE ISOTOPIQUE

Cœur & Chimiothérapie

DR. Boumediene LACHACHI
Cabinet d'Imagerie Scintigraphique
SIDI BEL ABBES

MARS 2018

Published Ahead of Print on May 11, 2015 as 10.1200/JCO.2014.58.9465
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2014.58.9465

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

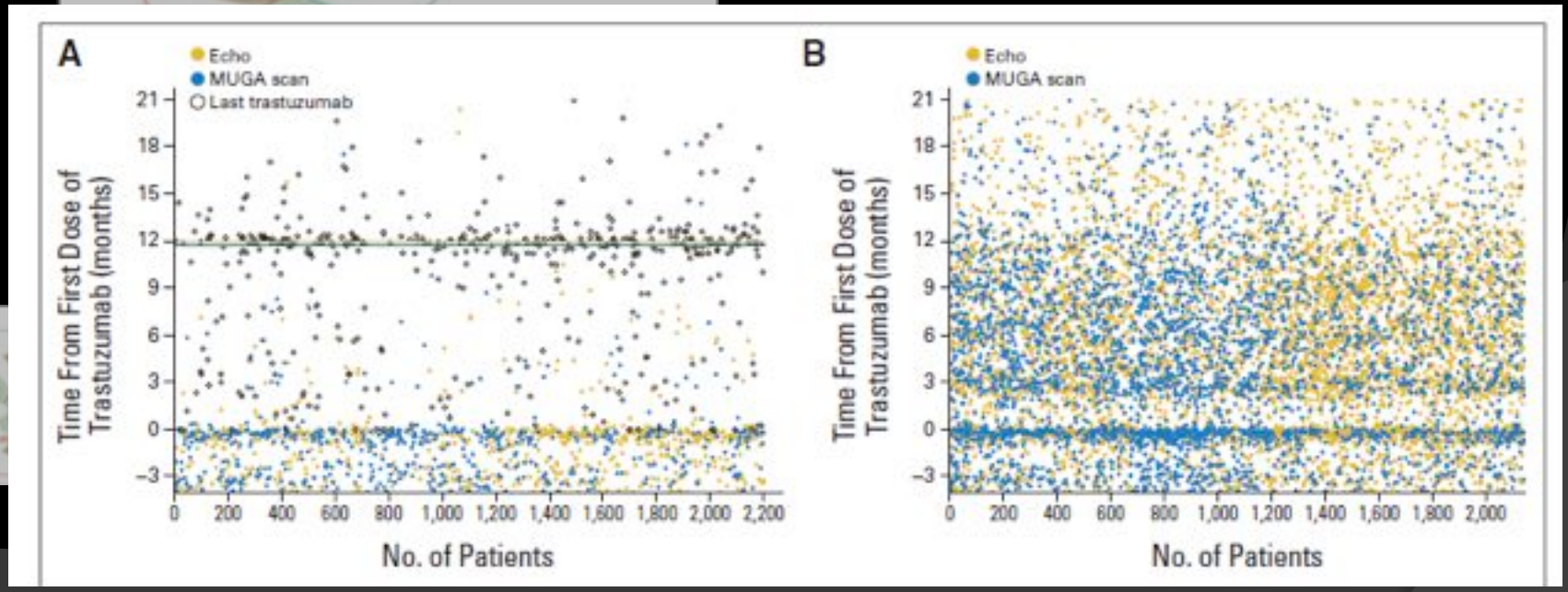
Cardiac Monitoring During Adjuvant Trastuzumab-Based Chemotherapy Among Older Patients With Breast Cancer

All authors: The University of Texas MD Anderson Cancer Center, Houston, TX.

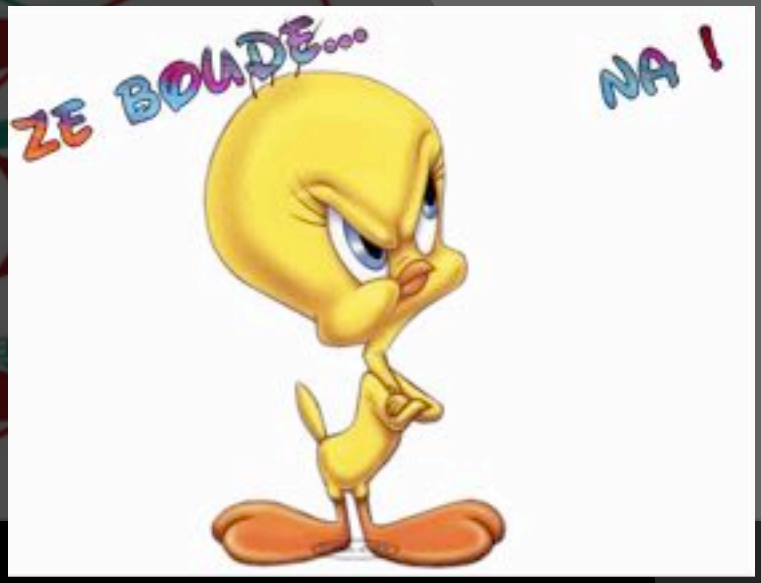
Published online ahead of print at www.jco.org on May 11, 2015.

Mariana Chavez-MacGregor, Jiangong Niu, Ning Zhang, Linda S. Elting, Benjamin D. Smith, Jose Banchs, Gabriel N. Hortobagyi, and Sharon H. Giordano

Association Nationale de Médecine Nucléaire Libérale



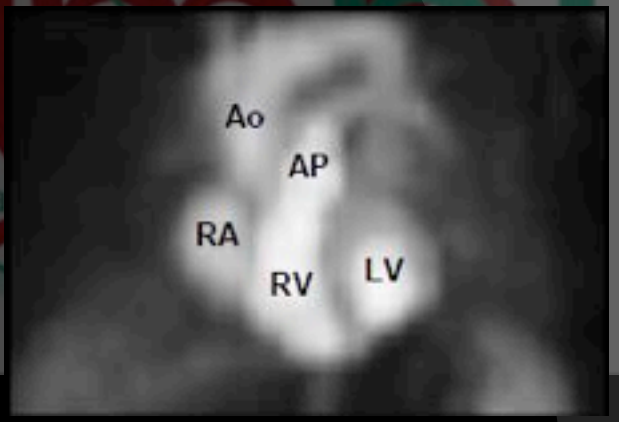
Pourquoi les oncologues et cardiologues boudent-ils la ventriculographie isotopique ?

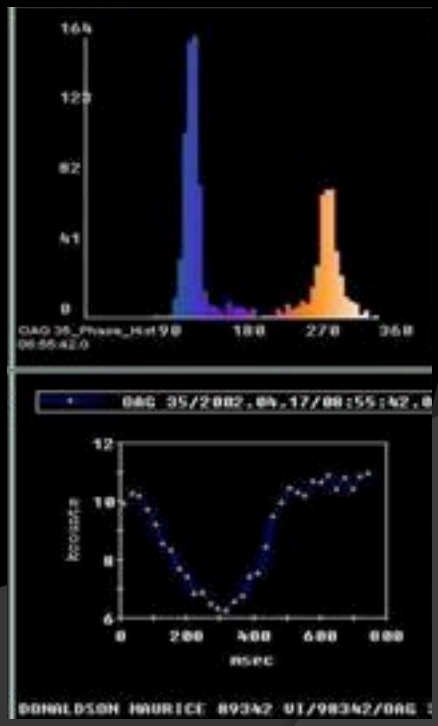




INTRODUCTION

- La Ventriculographie isotopique ou Angioscintigraphie ou FEV isotopique (MUGA, ERNA)
- Examen de médecine nucléaire depuis les années 70
- Permet l'étude de la fonction cardiaque
- FEVG entre autres…





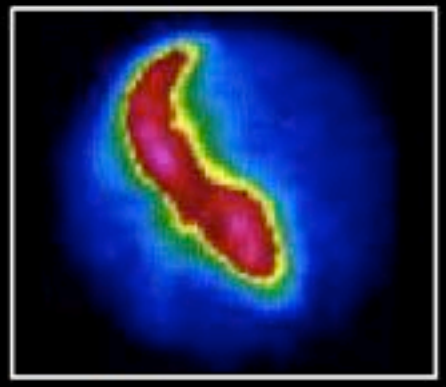
Radionuclide angiocardiography

planar imaging

(measured radioactivity is proportional to cavity volume)



equilibrium



first pass

tomographic

(3 dimensional imaging of the heart)



transaxial slice



volume rendered

TECHNIQUE

- Marquage des GR :

  Pyrophosphate stanneux + ^{99m}Tc

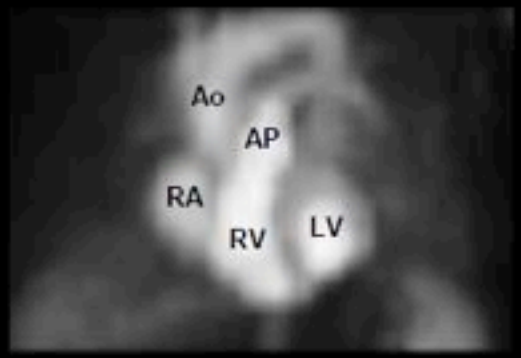
- Acquisition des images durant 10 minutes

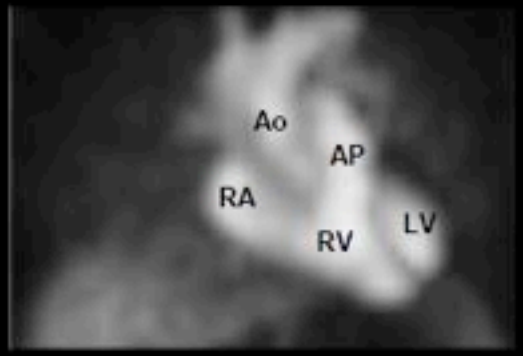
- Synchronisation à l'ECG : GATED

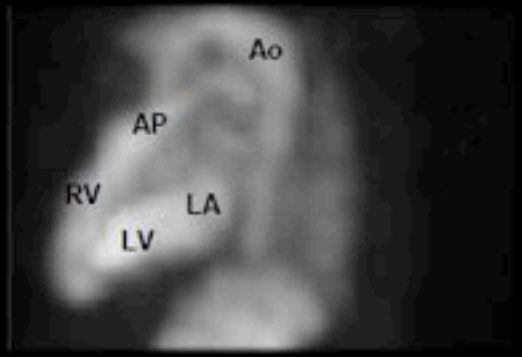
- Analyse des résultats

RESULTATS

ERNA: multiple views acquisitions

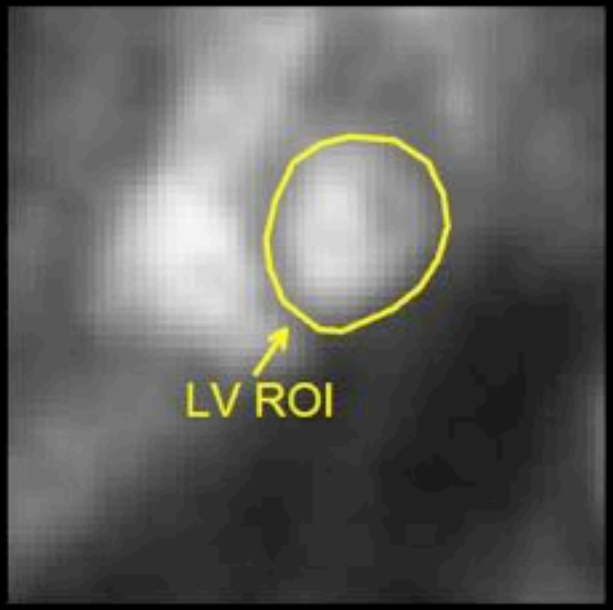


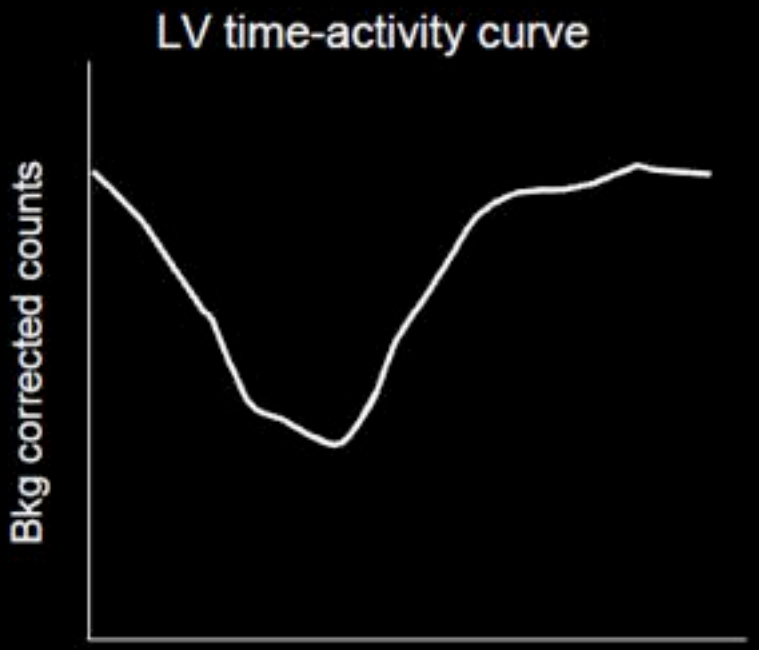




RESULTATS

ERNA: LVEF measurement



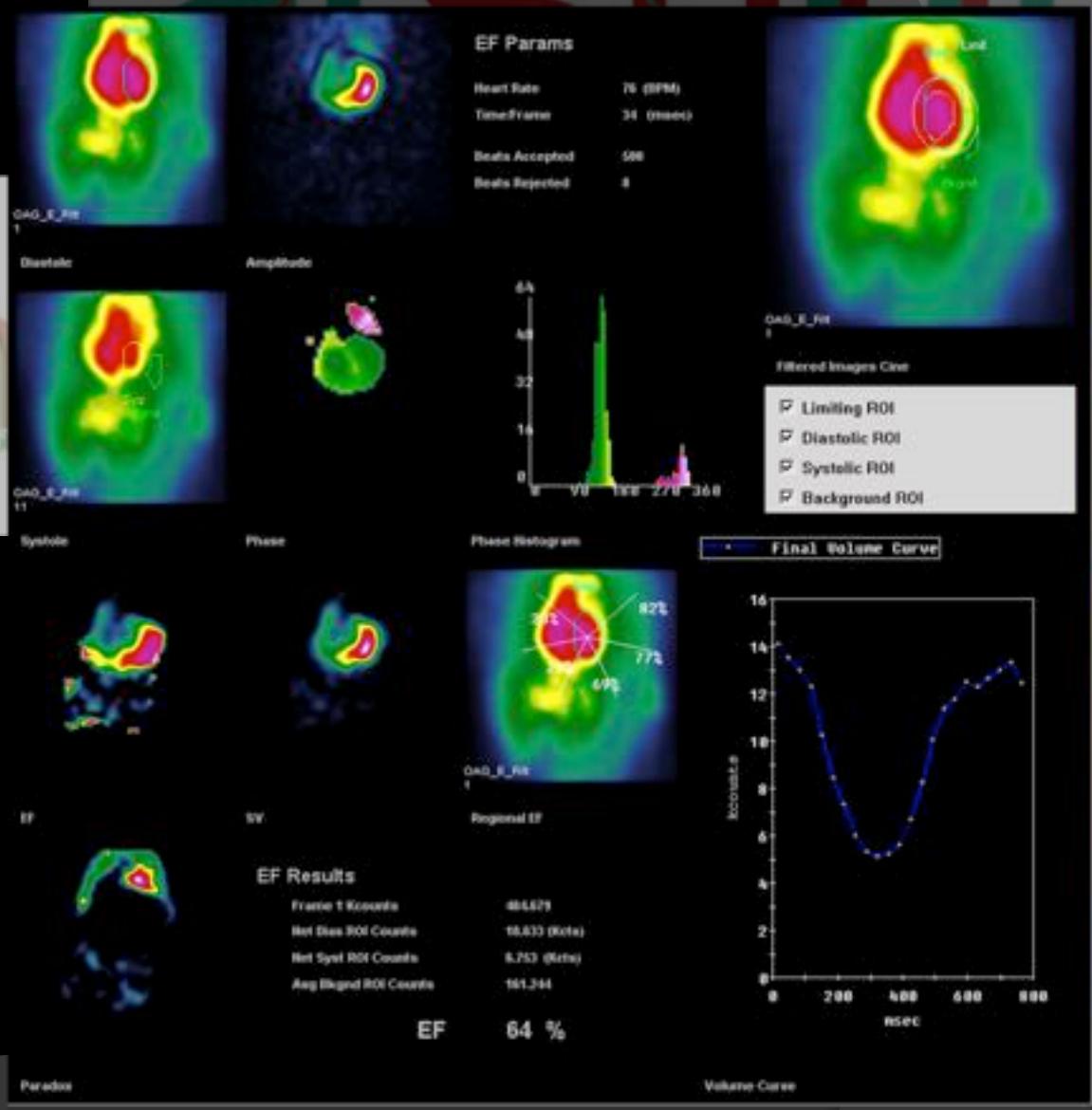


NO GEOMETRIC ASSUMPTION.
Counts measured in LV ROI after background correction are directly proportional to LV volume.

$$LVEF = \frac{ED\ cts - ES\ cts}{ED\ cts}$$

RESULTATS

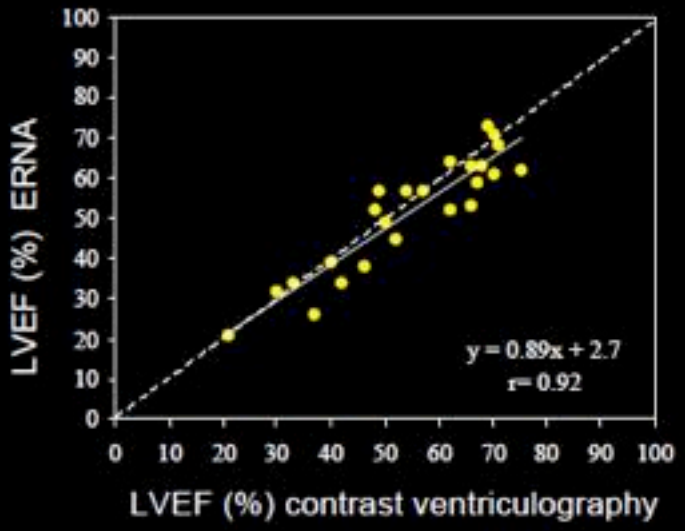
FEVG
Volume Télé Diastolique
Volume Télé Systolique
Courbe volumique du VG
Images paramétriques :
Amplitude et Phase



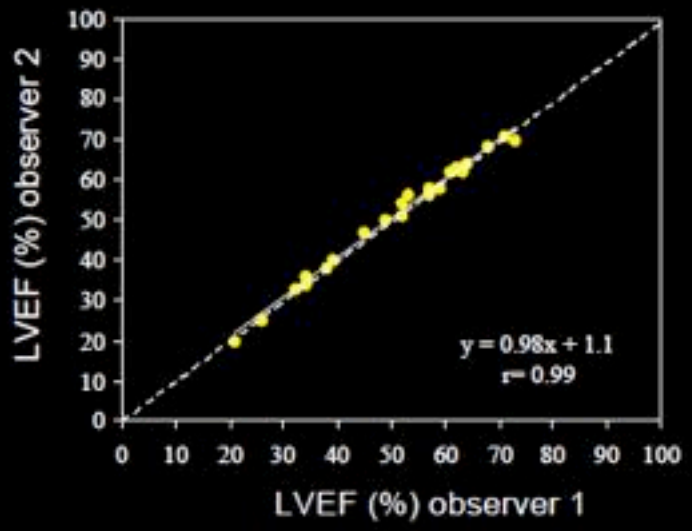
VALIDATION CLINIQUE

ERNA LVEF: LVEF measurement

correlation with
contrast ventriculography



inter observer
reproducibility



(Pfisterer, et al. 1979)

INDICATIONS

- Coronaropathies
- Insuffisance Cardiaque
- Mesure des délais de contraction : DAVD
- Les maladies valvulaires

- **Chimiothérapie : évaluation de la fonction ventriculaire avant, pendant et après traitement**

CŒUR ET CHIMIOTHERAPIE

- Arsenal thérapeutique de plus en plus complexe
- Complications cardio-vasculaires

TABLEAU 1 - LISTE DES DROGUES À RISQUE DE CARDIOTOXICITÉ D'APRÈS YEH (8) ; INCIDENCE DE LA CARDIOTOXICITÉ ET FRÉQUENCE D'UTILISATION.

Type d'agents	Incidence (%)	Fréquence d'utilisation
Anthracyclines		
• Doxorubicine (Adriamycine®)	3-26	+++
• Épirubicine (Ellence®)	0,9-3,3	++
• Idarubicine (Idamycin® PFS)	5-18	+
Agents alkylants		
• Cyclophosphamide (Cytoxan®)	7-28	+++
• Ifosfamide (Ifex®)	17	+++
Agents antimicrotubule		
• Clofarabine (Clolar®)	27	+
• Docétaxel (Taxotere®)	2,3-8	++
Anticorps monoclonaux		
Inhibiteurs des tyrosines kinases		
• Bévacizumab (Avastin®)	1,7-3	++
• Trastuzumab (Herceptine®)	2-28	++
Inhibiteur protéasome		
• Bortézomib (Velcade®)	2-5	++
Inhibiteurs des tyrosines kinases		
• Dasatinib (Sprycel®)	2-4	++
• Mésilate d'imatinib (Gleevec®)	0,5-1,7	+
• Lapatinib (Tykerb®)	1,5-2,2	+
• Sunitinib (Sutent®)	2,7-11	+++

TABLEAU 2 - LES DIFFÉRENTS MÉCANISMES DE CARDIOTOXICITÉ TYPE I ET TYPE II, D'APRÈS (16).

	Chimiothérapie type I	Chimiothérapie type II
Agents	Doxorubicine	Trastuzumab
Mécanisme	Formation de radicaux libres, stress oxydatif	Blocage de Erb B2
Dommages	Structurels, apoptose cellulaire	Non structurels
Ultrastructure (biopsie)	Modification tissulaire Nécrose	Pas de modification
Effet dose	Cumulatif, dose dépendant	Non dose dépendant
Devenir dysfonction VG	Irréversible, forte probabilité de récidive	Haute probabilité de récupération en 2 à 4 mois

CŒUR ET CHIMIOTHERAPIE

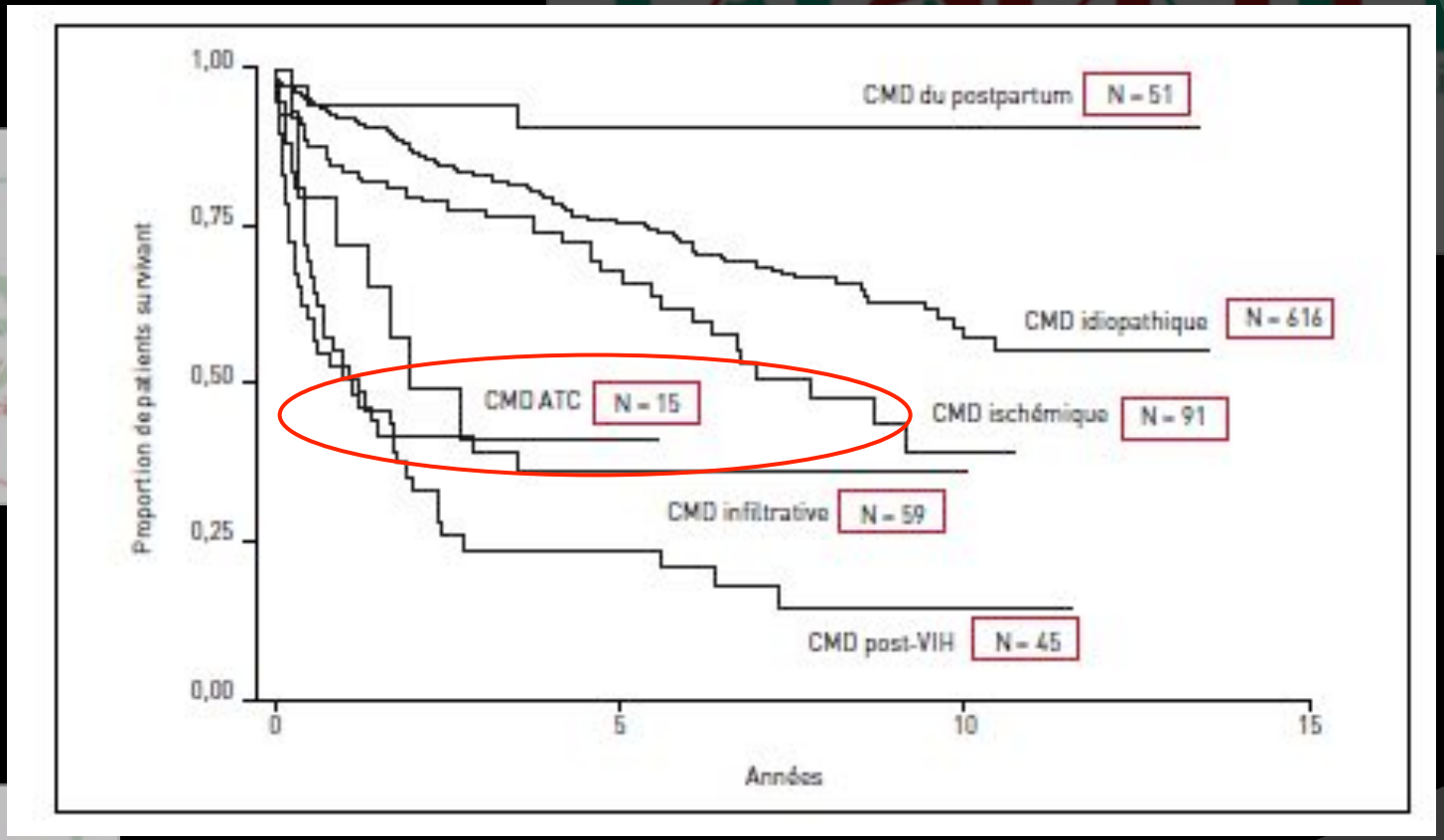


FIGURE 2 - Pronostic des différentes cardiomyopathies. CMD : cardiomyopathie ; ATC : anthracyclines.

CŒUR ET CHIMIOTHERAPIE

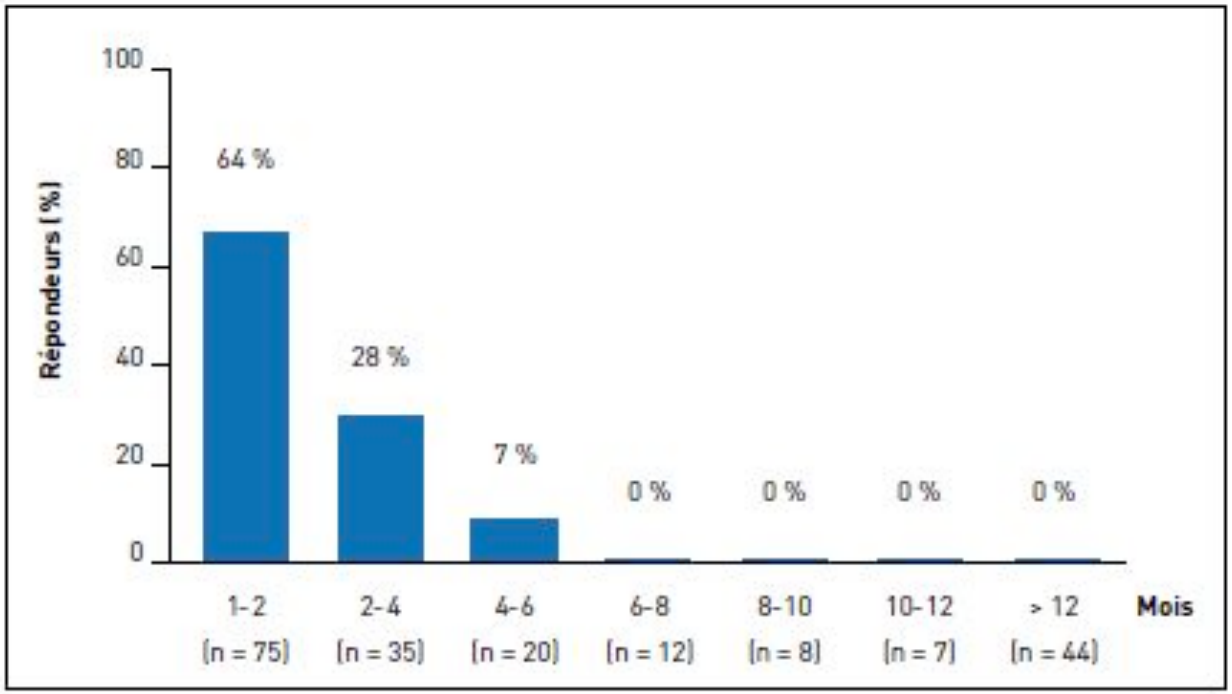
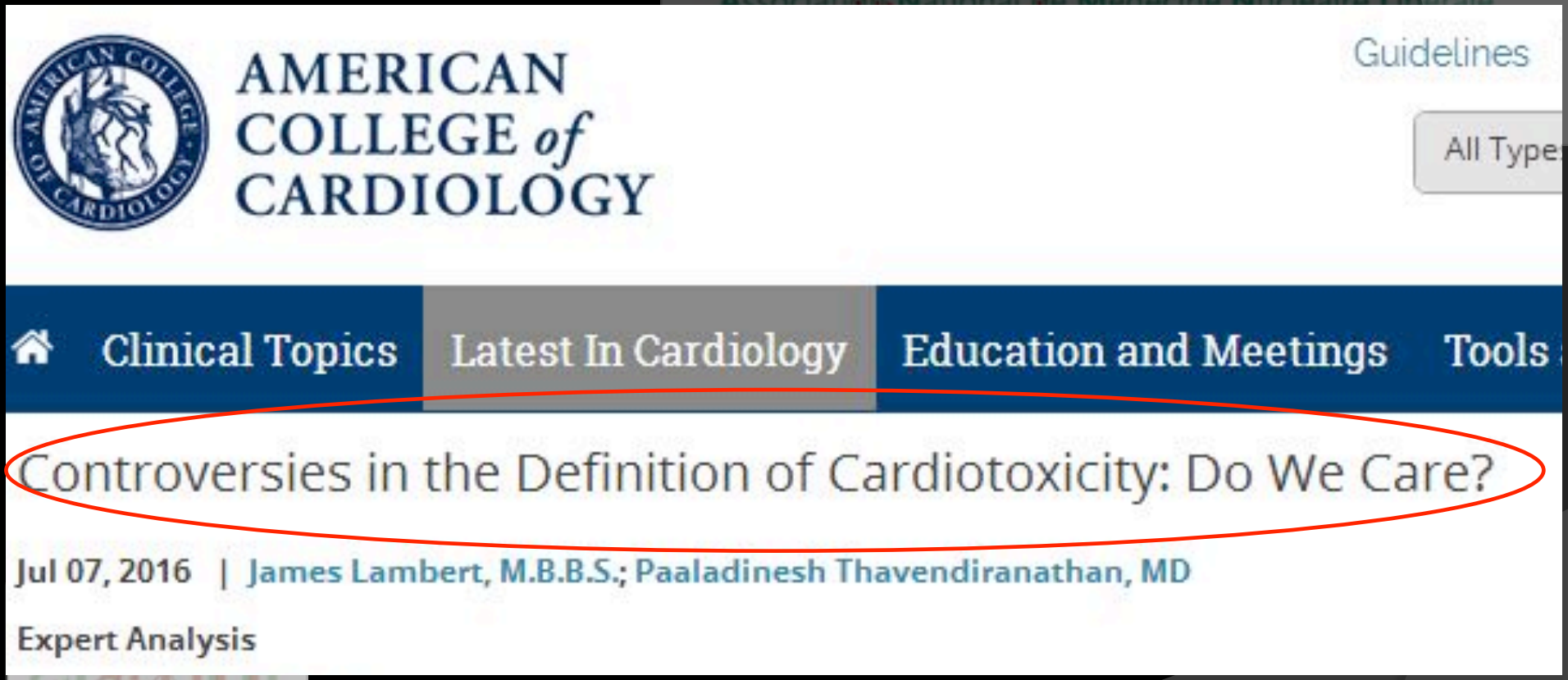


FIGURE 1 - Pourcentage de répondeurs au traitement à visée cardiaque en fonction du délai de mise en route du traitement après le diagnostic de cardiotoxicité, d'après (12).

CARDIOTOXICITE : Comment la définir ?



Controversies in the Definition of Cardiotoxicity: Do We Care?

Jul 07, 2016 | James Lambert, M.B.B.S.; Paaladinesh Thavendiranathan, MD

Expert Analysis

Table 1: Definitions of Cardiotoxicity

	Definition	Modality of Measurement	Chemotherapy Agents	Comments
Alexander et al.[22]	Mild: Decline in LVEF > 10% Moderate: Decline in LVEF > 15% to final LVEF < 45% Severe: congestive HF	Multigated acquisition (MUGA) scan	Anthracycline	
Schwartz et al.[23]	Decline in LVEF > 10% to final LVEF < 50%	MUGA scan	Anthracycline	

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Guidelines

All Type

Clinical Topics | Latest In Cardiology | Education and Meetings | Tools

Controversies in the Definition of Cardiotoxicity: Do We Care?

Jul 07, 2016 | James Lambert, M.B.B.S.; Paaladinesh Thavendiranathan, MD

Expert Analysis

Cardiac Review and Evaluation Committee[24]	1. Cardiomyopathy characterized by a decrease in LVEF globally or more severe in the septum 2. Sign and symptoms of HF 3. Decline of EF ≥5% to final ejection fraction < 55% with symptoms of congestive HF 4. Asymptomatic decline of LVEF ≥ 10% to final ejection fraction < 55%	MUGA scan and echocardiogram	Trastuzumab +/- Anthracycline	
Common Terminology Criteria for Adverse Events, version 4.03 (HF, left ventricular dysfunction)[56]		Not defined	N/A	Other definitions included such as troponin and clinical HF

EXPERT CONSENSUS STATEMENT

Expert Consensus for Multimodality Imaging Evaluation of Adult Patients during and after Cancer Therapy: A Report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging

Juan Carlos Plana, MD, FASE, Chair, Maurizio Galderisi, MD, FESC, Co-Chair, Ana Barac, MD, PhD, Michael S. Ewer, MD, JD, Bonnie Ky, MD, FASE, Marielle Scherrer-Crosbie, MD, PhD, FASE, Javier Ganame, MD, PhD, FASE, Igal A. Sebag, MD, FASE, Deborah A. Agler, RCT, RDCS, FASE, Luigi P. Badano, MD, PhD, FESC, Jose Banchs, MD, FASE, Daniela Cardinale, MD, PhD, FESC, Joseph Carver, MD, Manuel Cerqueira, MD, Jeanne M. DeCara, MD, FASE, Thor Edvardsen, MD, PhD, FESC, Scott D. Flamm, MD, MBA, Thomas Force, MD, Brian P. Griffin, MD, Guy Jerusalem, MD, PhD, Jennifer E. Liu, MD, FASE, Andreia Magalhães, MD, Thomas Marwick, MBBS, PhD, MPH, Liza Y. Sanchez, RCS, FASE, Rosa Sicari, MD, PhD, FESC, Hector R. Villarraga, MD, FASE, and Patrizio Lancellotti, MD, PhD, FESC, *Cleveland, Ohio; Naples, Padua, Milan, and Pisa, Italy; Washington, District of Columbia; Houston, Texas; Philadelphia, Pennsylvania; Boston, Massachusetts; Hamilton, Ontario and Montreal, Quebec, Canada; Chicago, Illinois; Oslo, Norway; Liege, Belgium; New York, New York; Lisbon, Portugal; Hobart, Australia; Rochester, Minnesota*

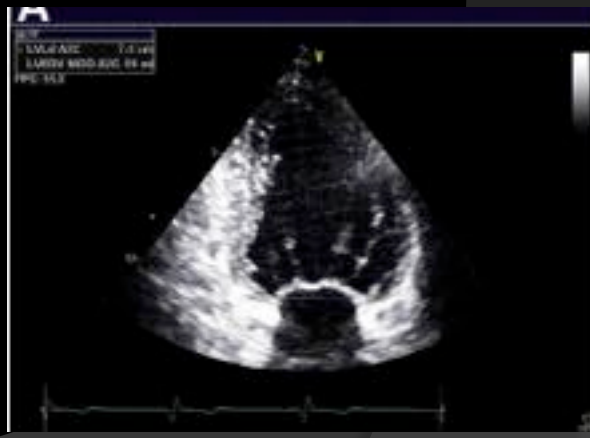
(J Am Soc Echocardiogr 2014;27:911-39.)

Keywords: Chemotherapy, Doxorubicin, Trastuzumab, Left ventricular dysfunction, Three-dimensional echocardiography, Early detection, Strain, Biomarkers

ECHCARDIOGRAPHIE

- Méthode de Choix
- Disponible et peu onéreuse
- Mesure de la FEVG par méthode Simpson
- Limites :
  - Echogénéicité
  - Pace maker
  - Reproductibilité (CV : 8 à 10%)





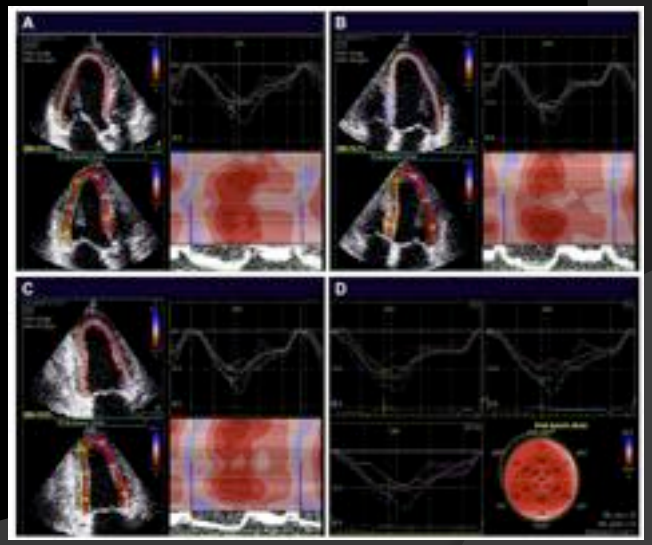
J Am Soc Echocardiogr 2014;27:911-39

ECHOCARDIOGRAPHIE

- Echo 3D
  - Méthode révolutionnaire
  - Plus de précision de la mesure volumique
  - Technique non encore répondue



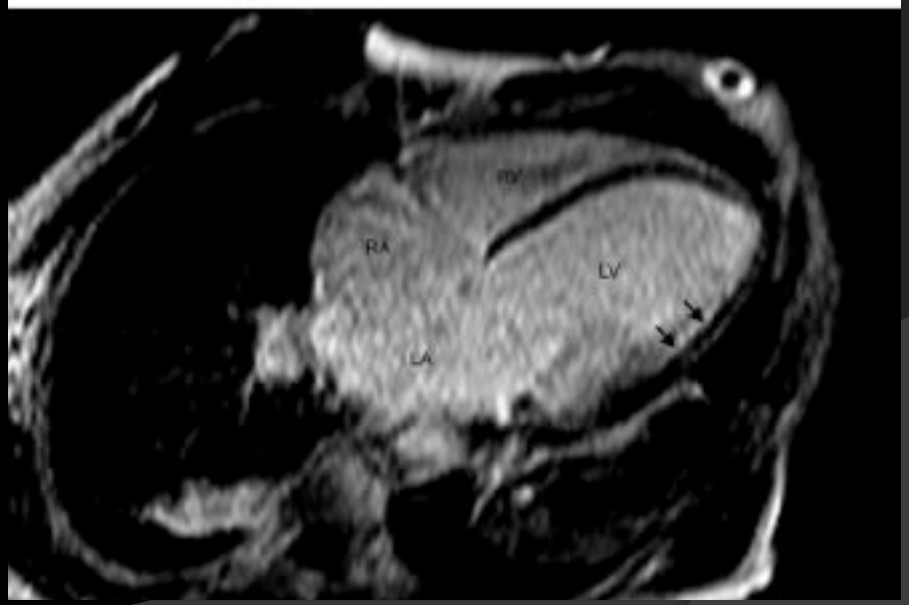
- GLS : Global Strain
  - Détection précoce de la cardiotoxicité
  - Pas de consensus



J Am Soc Echocardiogr 2014;27:911-39

IRM Cardiaque

- Méthode référence dans la mesure des volumes ventriculaires (VG et VD)
- Permet une analyse structurelle : Fibrose myocardique
- Limites :
  - Disponibilité
  - Courbe d'apprentissage



J Am Soc Echocardiogr 2014;27:911-39

VENTRICULOGRAPHIE

patients with subclinical LV dysfunction after trastuzumab.[200] Of 42

The MUGA technique for monitoring anthracycline-induced CTRCD has been standardized, shown to be highly reproducible, and widely available and effectively applied in academic centers, community hospitals, and physicians' offices.[33] On the basis of these findings, MUGA has been widely used in general clinical practice as well as in the efficacy trials for development of new chemotherapy agents for all tumor types.[209] Advantages of MUGA in evaluation of patients during or after cancer therapy include the following:

toring by MUGA to detect an asymptomatic decline in LVEF was preferable to waiting for the development of symptoms of congestive HF

lators. The technique is widely available, and cost is comparable with that of alternative modalities.

J Am Soc Echocardiogr 2014;27:911-39

VENTRICULOGRAPHIE

- Inconvénients :
  - Irradiation : environ 5 mSv (2 fois l'exposition naturelle)
  - Arythmies
  - Pas d'information structurelle

European Heart Journal (2016) **37**, 2768–2801
doi:10.1093/eurheartj/ehw211

ESC CPG POSITION PAPER

2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines

The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC)

CARDIOTOXICITE : Facteurs de risque

Table 2 Factors associated with risk of cardiotoxicity following treatment with anthracyclines[a]

Risk factors
• Cumulative dose
• Female sex
• Age
- >65 years old
- Paediatric population (<18 years)
• Renal failure
• Concomitant or previous radiation therapy involving the heart
• Concomitant chemotherapy
- alkylating or antimicrotubule agents
- immuno- and targeted therapies
• Pre-existing conditions
- Cardiac diseases associating increased wall stress
- Arterial hypertension
- Genetic factors

[a]Anthracyclines (daunorubicin, doxorubicin, epirubicin, idarubicin) or anthracenedione (mitoxantrone).

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European Heart Journal (2016) **37**, 2768–2801
doi:10.1093/eurheartj/ehw211

Table 3 Factors associated with risk of cardiotoxicity following anti-HER2 compounds and VEGF inhibitors[70–72]

Agent	Risk factors
Anti-HER2 compounds	
- Antibodies - Trastuzumab - Pertuzumab - T-DM1 - Tyrosine kinase inhibitor - Lapatinib	• Previous or concomitant anthracycline treatment *(short time between anthracycline and anti-HER2 treatment)* • Age (>65 years) • High BMI >30 kg/m² • Previous LV dysfunction • Arterial hypertension • Previous radiation therapy
VEGF inhibitors	
- Antibodies - Bevacizumab - Ramucirumab	Pre-existing HF, significant CAD or left side VHD (e.g. mitral regurgitation), chronic ischaemic cardiomyopathy • Previous anthracycline
- Tyrosine kinase inhibitors - Sunitinib - Pazopanib - Axitinib - Neratinib - Afatinib - Sorafenib - Dasatinib	• Arterial hypertension • Pre-existing cardiac disease

BMI = body mass index; CAD = coronary artery disease; HER2 = human epidermal growth factor receptor 2; HF = heart failure; MI = myocardial infarction; VEGF = vascular endothelial growth factor; VHD = valvular heart disease.

CARDIOTOXICITE : Outils DC

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.

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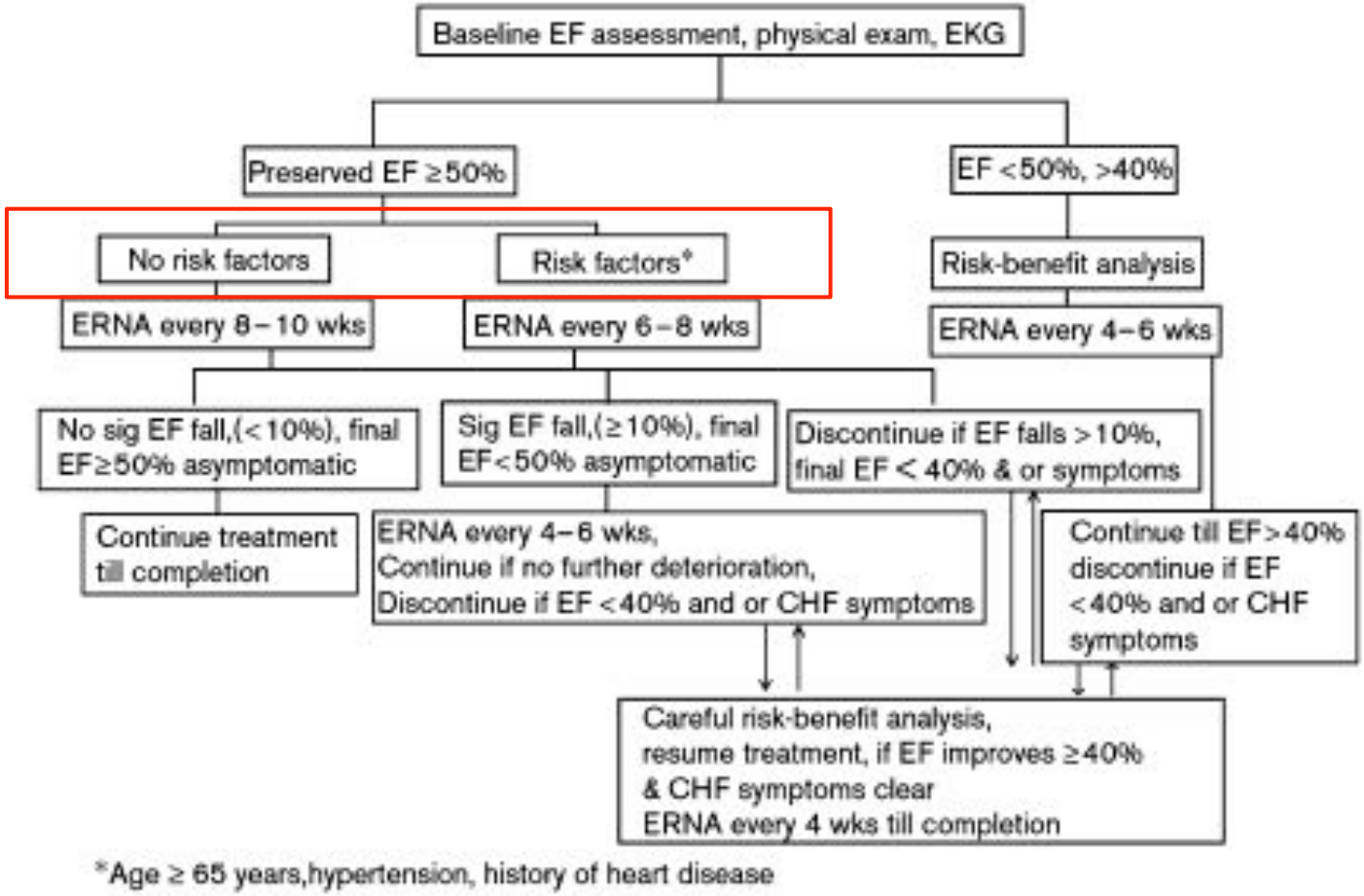
European Heart Journal (2016) **37**, 2768–2801
doi:10.1093/eurheartj/ehw211

Recommandations : choix de l'examen ?

- Le même examen doit être utilisé pour le suivi de la fonction cardiaque. Le changement est fortement déconseillé
- L'examen avec la meilleure reproductibilité est préféré
- Sont préférés, les examens avec des informations cliniques supplémentaires (en plus de la FEVG).

European Heart Journal (2016) **37**, 2768–2801
doi:10.1093/eurheartj/ehw211

ALGORITHME MUGA



A proposed algorithm for monitoring trastuzumab cardiotoxicity.

Journal of Nuclear Cardiology Volume 20, Number 3;443-64

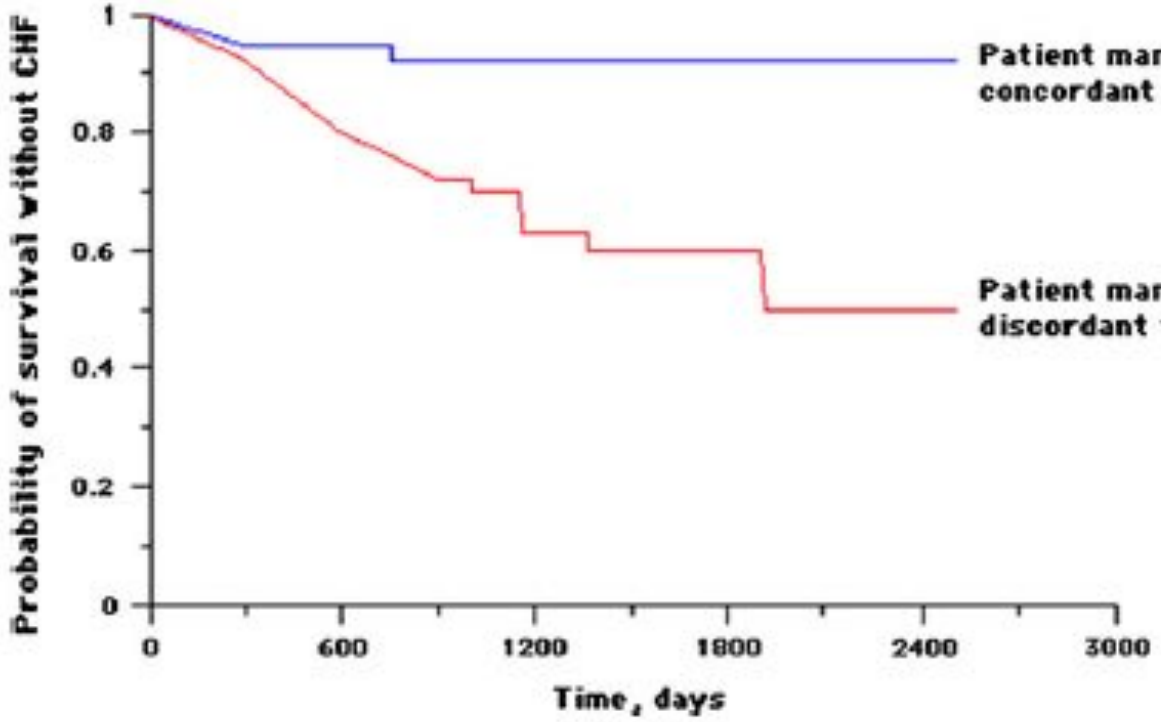


Figure 1. Guidelines prevent doxorubicin cardiotoxicity. Kaplan-Meier plot describes the probability of survival without clinical CHF in patients whose management was either concordant or discordant with the guideline criteria for monitoring patients receiving doxorubicin. Patients managed by the guidelines had a fourfold reduction in the incidence of clinical CHF independent of other predictor variables ($P < .01$). When CHF did occur with guideline concordant management, severity of CHF was no worse than mild. By comparison, the severity of clinical CHF was worse than mild in the majority in the group of patients whose management was discordant with the guidelines. *Source* Ref. 8.

Journal of Nuclear Cardiology
Volume 20, Number 3;443-64

Que peut apporter la ventriculographie en plus de la FEVG ?

JNM
The Journal of Nuclear Medicine

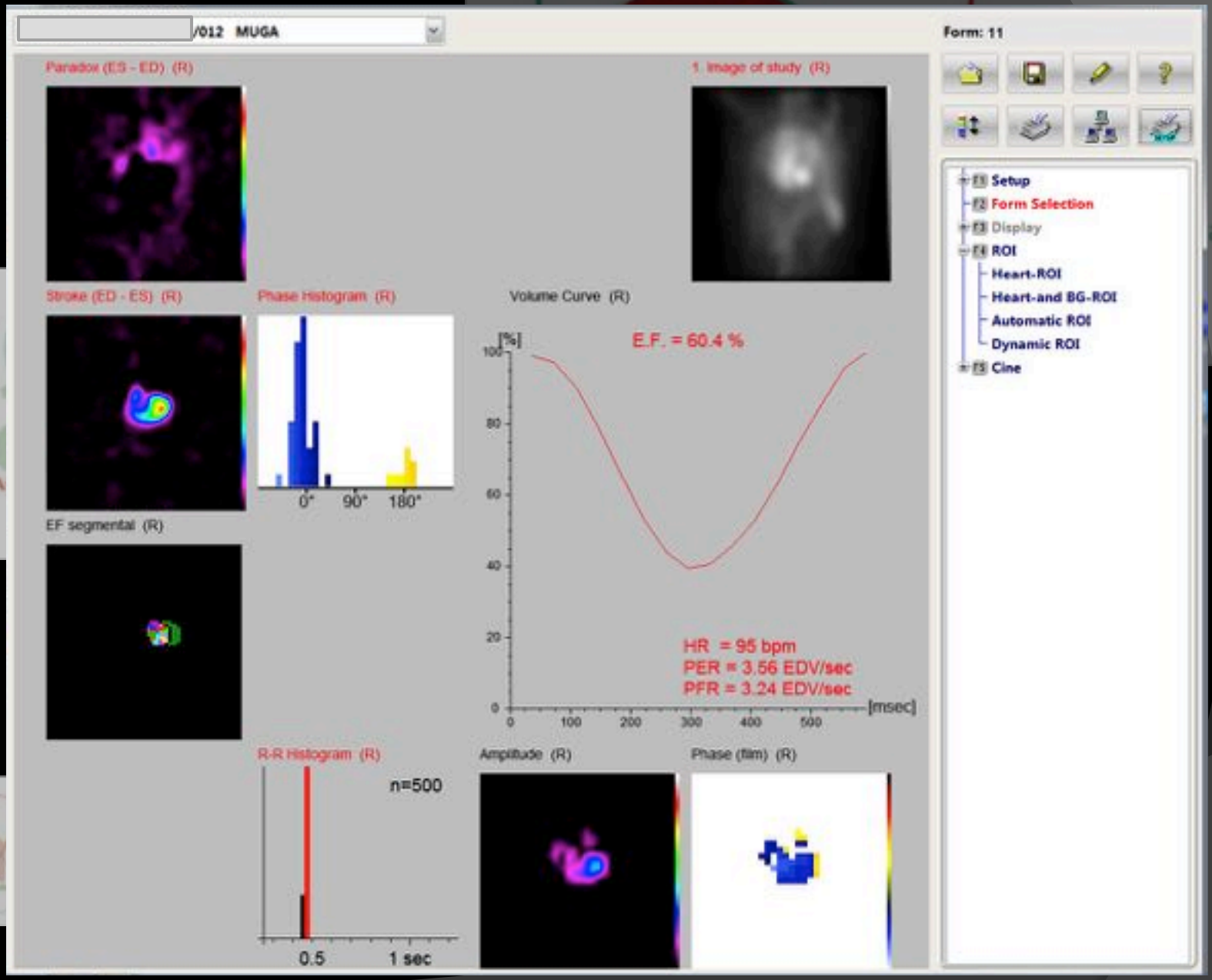
Assessment of the effect of cardiotoxic chemotherapeutic agents on the different phases of the cardiac cycle using multiple-gated acquisition scan and volume time curves can predict cardiotoxicity earlier than evaluation ejection fraction alone

Osama Gomaa[1], Dimitrios Kalkanis[1], Shabbir Ezuddin[1], Mike Georgiou[1], Efrosyni Sfakianaki[1], Charif Sidani[1], Mohamed Mohamed[2], Aldo Serafini[1] and George Sfakianakis[1]

J Nucl Med, May 2011, 52-1128

- 27 témoins (49±9 ans) Vs 51 patients (52±10 ans) traités par chimio (Doxorubicine, Trastuzumab ou les deux).
- MUGA avant et 3 mois après traitement
- Pas de différence de FEVG entre les deux groupes (P value >0.05)
- Différence significative des temps de remplissage diastolique (P value <0.05)
- **Les données de la courbe volumique peuvent détecter de façon plus précoce que la FEVG une cardiotoxicité**

J Nucl Med, May 2011, 52-1128


/012 MUGA
Form: 11
Paradox (ES - ED) (R)
1. Image of study (R)
Stroke (ED - ES) (R)
Phase Histogram (R)
Volume Curve (R)
E.F. = 60.4 %
[%]
100
80
60
40
20
0
0°
90°
180°
EF segmental (R)
HR = 95 bpm
PER = 3.56 EDV/sec
PFR = 3.24 EDV/sec
0
100
200
300
400
500
[msec]
R-R Histogram (R)
n=500
Amplitude (R)
Phase (film) (R)
0.5
1 sec
F1 Setup
F2 Form Selection
F3 Display
F4 ROI
Heart-ROI
Heart-and BG-ROI
Automatic ROI
Dynamic ROI
F5 Cine

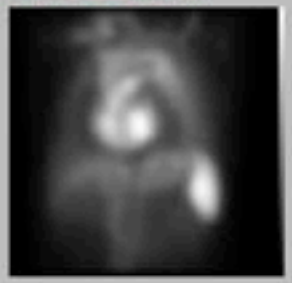
021 MUGA

Form: 11

Paradox (ES - ED) (R)



1. Image of study (R)

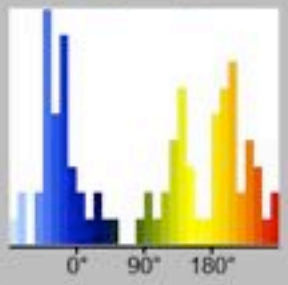


- F1 Setup
- F2 Form Selection
- F3 Display
- F4 ROI
  - Heart-ROI
  - Heart-and BG-ROI
  - Automatic ROI
  - Dynamic ROI
- F5 Cine

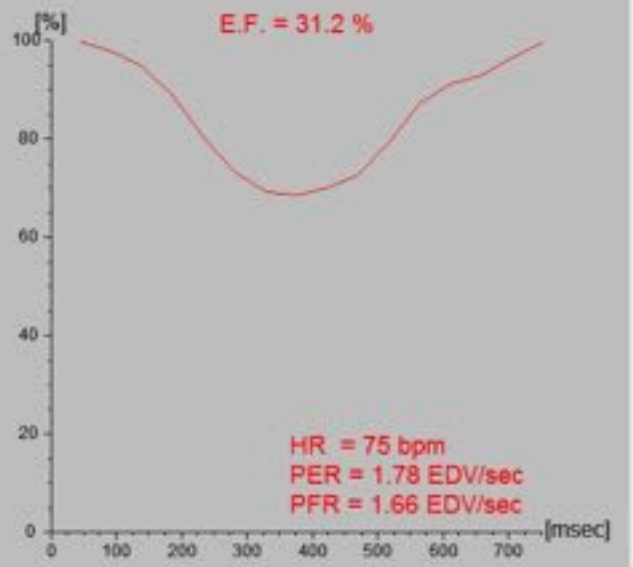
Stroke (ED - ES) (R)



Phase Histogram (R)



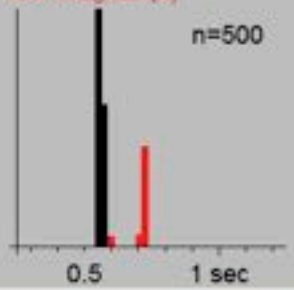
Volume Curve (R)



EF segmental (R)



R-R Histogram (R)



Amplitude (R)



Phase (film) (R)



VENTRICULOGRAPHIE

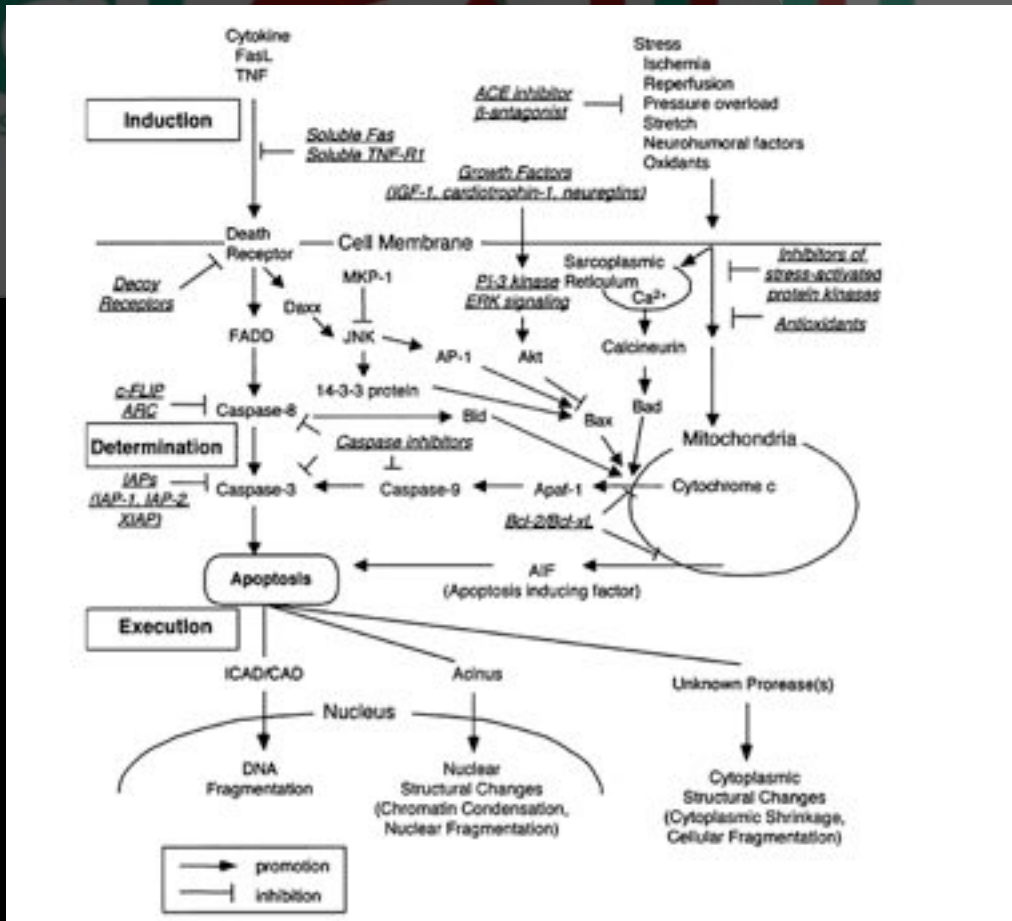
1. LVEF > 50% at baseline
   a. Measurement at 250 to 300 mg/m^2
   b. Measurement at 450 mg/m^2
   c. Measurement before each dose above 450 mg/m^2
   d. Discontinue therapy if LVEF decreases by ≥10% from baseline and LVEF ≤ 50%
2. LVEF < 50% at baseline
   a. Do not treat if LVEF is <30%
   b. Serial measurement before each dose
   c. Discontinue therapy if LVEF decreases by ≥10% from baseline or LVEF ≤ 30%

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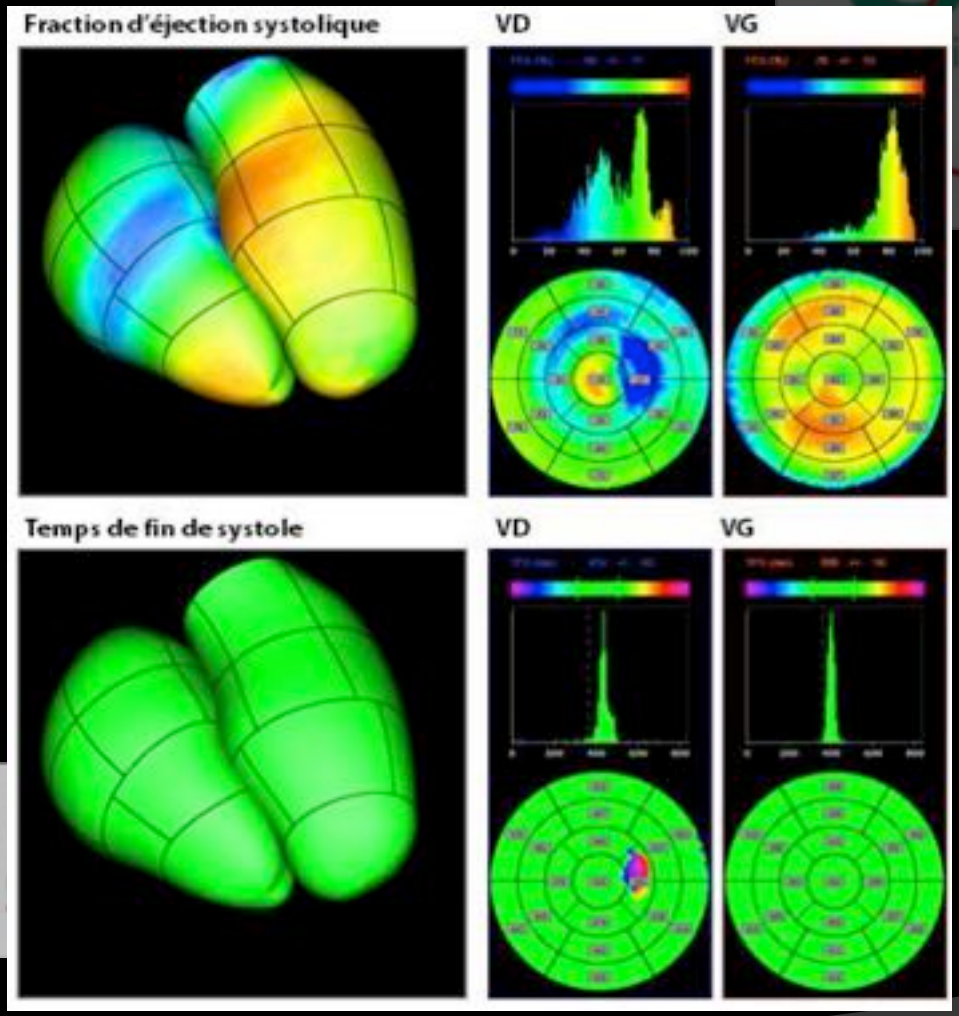
AVENIR

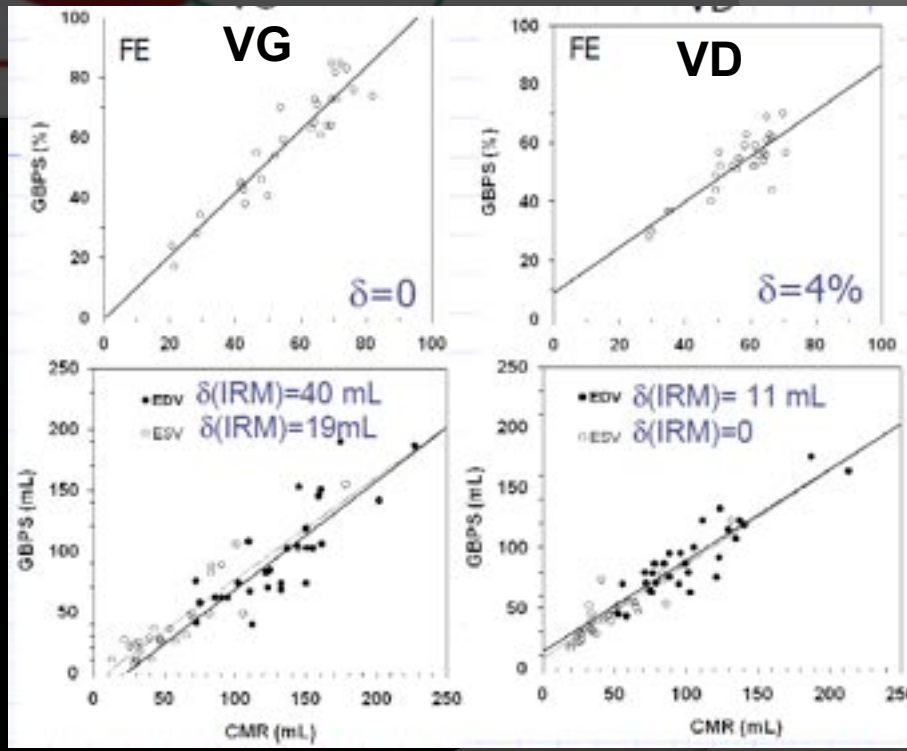
Technique	Tracer
Mechanical pump function	^{99m}Tc ERNA (planar)
	^{99m}Tc ERNA (SPECT)
Neuronal imaging	^{123}I MIBG
Imaging necrosis/ cell death	^{111}In antimyosin
Imaging cell death/ apoptosis	^{99m}Tc annexin V
Fatty acid use	^{123}I BMIPP
	^{123}I paraphenyl pentadecanoic acid
Therapeutic target imaging	^{111}In trastuzumab



Journal of Nuclear Cardiology
Volume 20, Number 3;443-64

VENTRICULOGRAPHIE 3D





Mariano-Goulart et al. J Nucl Med. 2007 ; 47: 1416-1423

KEY POINTS

- Adopter une démarche consensuelle dans le suivi des patients sous chimiothérapie cardiotoxique
- Nécessité d'un dépistage précoce
- Stratification du risque de cardiotoxicité
- La Ventriculographie : « examen reproductible »
- MUGA : FEVG pas que !