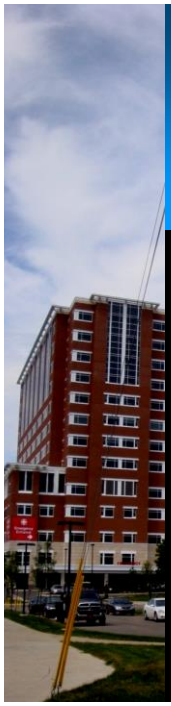

Expert Consensus for MMI Evaluation of Adult Patients During and After Cancer Rx

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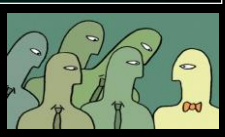
Assistant Chief, Division of Cardiovascular Medicine
Chair, Cardiac Imaging for the Academic Service Line

UK UNIVERSITY OF KENTUCKY

UK HealthCare Gill Heart Institute

6th Annual Echo Florida, October 2017

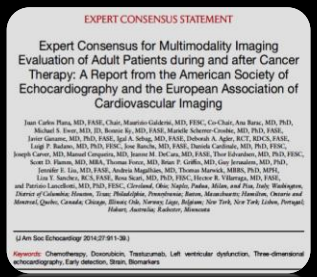
Disclosures



No Real or Potential Conflict of Interests for this Talk

"CTRCD"

J Am Soc Echocardiogr 2014;27:911-39


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

CTRCD CTRCD

Cancer Therapy Related Cardiac Dysfunction

CTRCD CTRCD

Outline

Cancer and the Cardiovascular Specialist

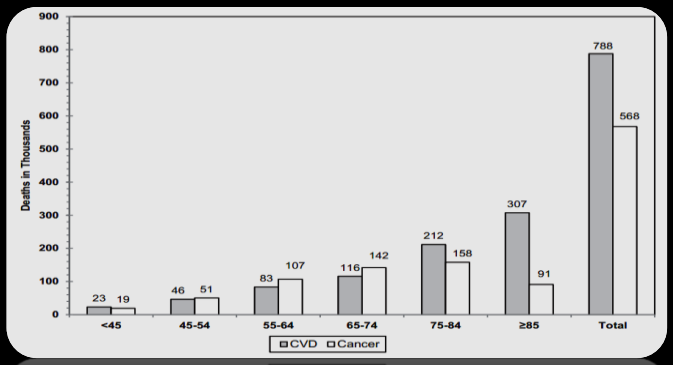
- Radiation therapy effects
- Chemotherapeutics (and the CTRCD definition)

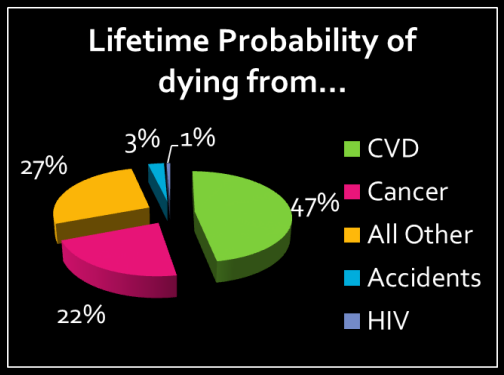
Complementary role of Multimodality Imaging

- Review of ASE / ESE Guidelines (#10 key points)
- Specific focus on Echo (3D, Speckle-tracking)

Case Example (impact of GLS)

Two most common Deadly Diseases





Nearly ~1 million pts / yr receive anthracycline Rx (a ~5% risk = 50,000)

AHA Heart Statistics. Circulation

QUESTION

Myocardial damage after anthracycline administration occurs when?

A. Within the first few hours of the initial dose
B. After 250 g/m2
C. Between 250-400 g/m2
D. After >400 g/m2
E. Highly variable & occasionally not at all

ANSWER

Myocardial damage after anthracycline administration occurs when?

A. ***Within the first few hours of the initial dose***
B. After 250 g/m2
C. Between 250-400 g/m2
D. After >400 g/m2
E. Highly variable & occasionally not at all

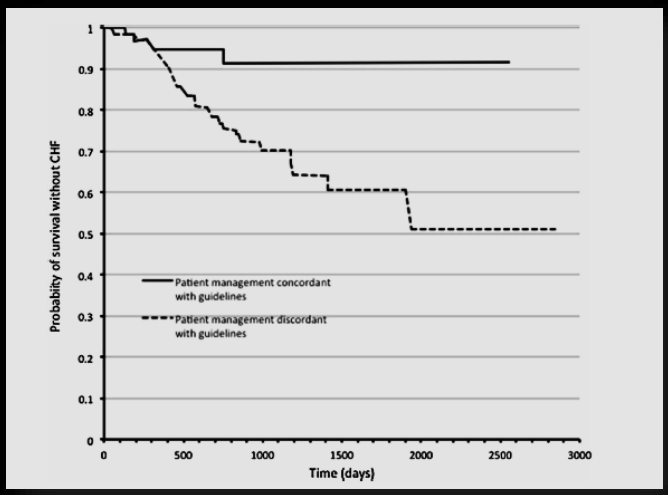
CHEMOTHERAPY history

- Myocardial damage is **immediate** after anthracycline Rx but ***significant cardiac reserve*** limits detection (EF)
- 1960's: life-saving chemotherapy causes cardiac toxicity
- Oncologists learned to *limit doses* to avoid this
- 1970's: serial EMB best Se/Sp
- **Natural improvement** in drugs **(*less doses*)** and **imaging (*MUGA / Echo*)** made **risk/benefit EMB** *unfavorable*
- Thus, *cardiac damage* may not be seen with routine testing or may require *years* after Rx (childhood survivors)

Balancing Act of Goals

ONCOLOGIST (*immediate*)

CARDIOLOGIST (*long term*)



MUGA / RNA

10 unit fall in LVEF or <50%

15% of high risk pts developed CHF within1Y after Rx

75 ……..1095 mg/M2 → **CHF +**

30 …….. 880 mg/M2 → **CHF -**

Total cumulative dose of Doxo causing CHF was not very different from doses that did not

KEY POINT #1 - definition

Highly effective chemo may cause CTRCD:

1. Type I CTRCD (e.g. anthracyclines)

- Dose dependent, cell apoptosis, irreversible
- Early detection & prompt Rx may prevent HF

2. Type II CTRCD (e.g. trastuzumab)

- Not dose dependent, no apoptosis, ~reversible

DEFINITION: CTRCD

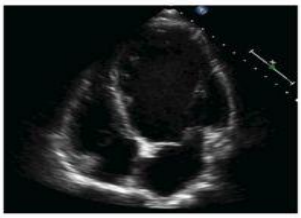
Universal LVEF Threshold

- Confirmed drop in LVEF >10 points to <53%
  - Need to confirm with REPEAT "*cardiac imaging*" 2-3 wks after initial study showing the fall in LVEF
- *Symptomatic vs Asymptomatic* CTRCD
- **Reversible** (to within 5% baseline)
- **Partial** (improved >10%; not to within 5% baseline)
- **Irreversible** (remains within 10% nadir)

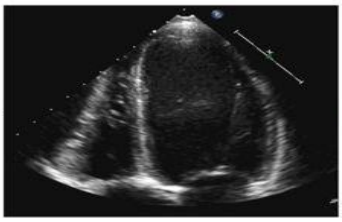
KEY POINT #2 – LV systole

- Echocardiography: **method of choice** for the evaluation *before, during,* and *after* cancer therapy
- Accurate calculation of LVEF should be done with the **best method** in your echo lab (3DE recommended)
- If 2DE, modified biplane Simpson's is recommended
- LVEF should be combined with **WMSI calculation**
- If no STE (GLS), **MAPSE** (M-mode) and/or **DTI (s')** of the mitral annulus is recommended

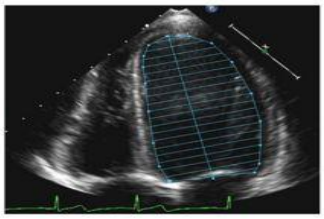
LVEF by 2DE often *fails to detect small changes in LV contractility*



1. Get a good Apical 4 chamber view

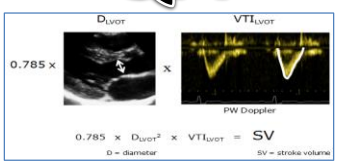


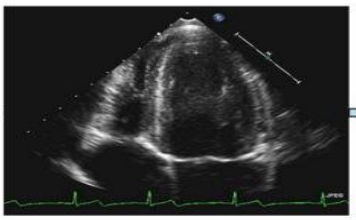
2. Zoom on the LV



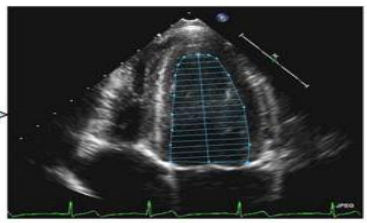
3. Trace the LV diastolic endocardial border

QA



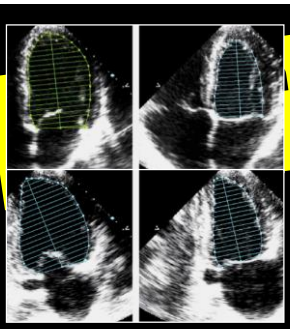


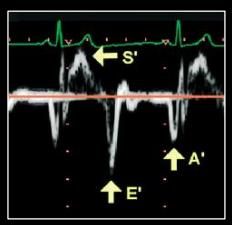
4. Roll the trackball to systole in the same cardiac cycle



5. Trace the LV systolic endocardial border

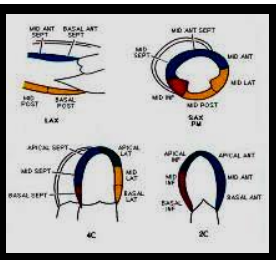
Reduced Ejection Fraction = extensive LV damage

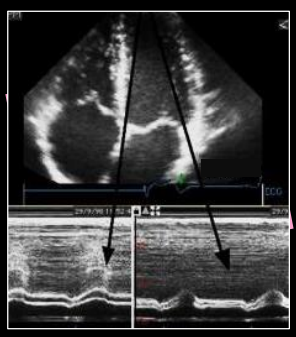




* 3DE

LV Systolic Function





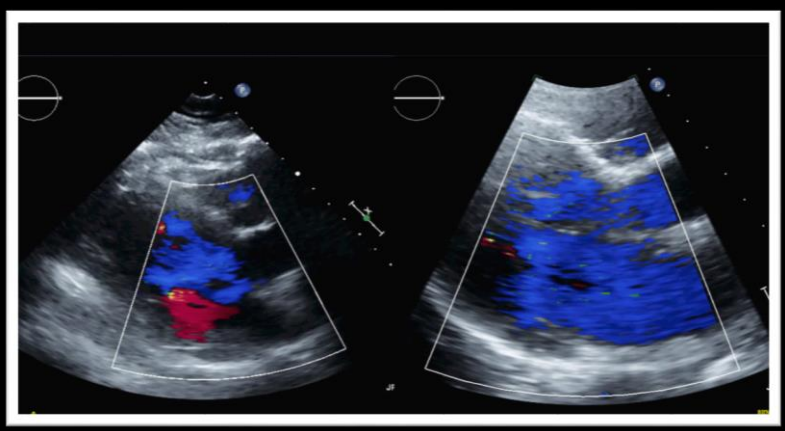
* GLS via 2D Strain / STE

KEY POINT #3 - Valves

- Valves should be carefully evaluated
- Patients with *baseline (or changing) valve findings during chemo* require careful re-evaluation with serial echo during and after the course of Rx

PATIENT CASE

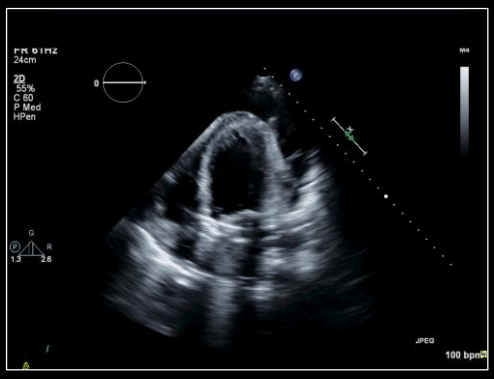
40F with multiple cycles of chemoRx and BMT



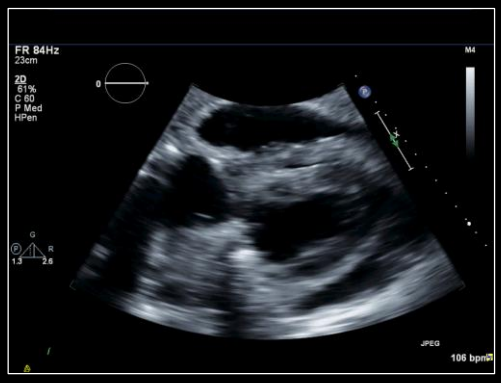
KEY POINT #4 - pericardium

- Pericardial disease: consider **metastasis** or effect from chemo and/or radiotherapy
- Pericardial effusion should be quantified / graded
- Echo / Doppler signs of **tamponade** should be investigated, particularly in *malignant effusions*
- **CMR: useful** to evaluate 1º cardiac tumors w/wo compromise of the pericardium; if 'constriction' *dx remains uncertain* after echocardiography

65F; Breast Ca; p-eff found on CT; SBP ~100

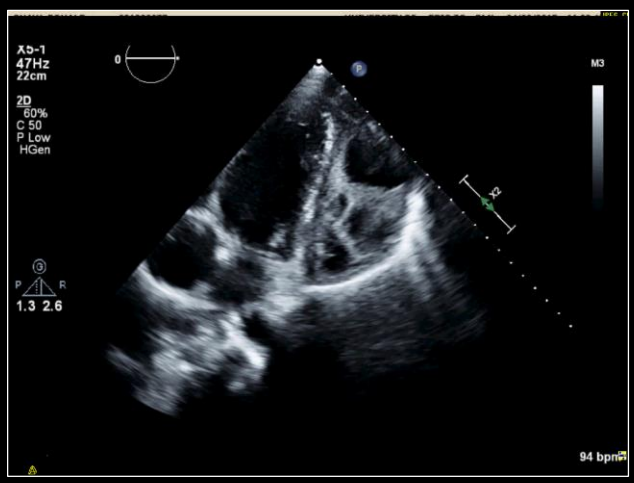


Ms Jones



Ms Smith

What about Ms. Williams?

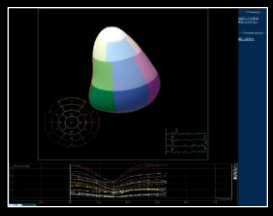


KEY POINT #5 – 3DE

- **3D echo** is the preferred technique for serial LVEF to detect CTRCD
- Advantages include better accuracy (detecting LVEF below LLN), reproducibility, and lower temporal variability compared with 2DE
- Costs, availability, reliance on image quality, and training currently limits wide application of 3DE

3D ECHOCARDIOGRAPHY

- Biplane Simpson similar to 3D if normal LV shape
  - In pts with LVEF <50% by CMR:
    - 3DE: sensitivity = 53%; False (-) rate 47%
    - 2DE: sensitivity = 25%; False (-) rate 75%



- 2D vs 3D serial evaluation of Chemo pts
  - **Reproducibility** 3DE **4.9%** (vs 2DE **10%**)
  - Lowest inter- & intra-variability and Highest test-retest

Armstrong GT, et al. J Clin Oncol 2012;30:2876-2884.
Thavendiranathan P, et al. J Am Coll Cardiol 2013;61:77-84.

Hot off the Presses… Lorenzini JASE 2017

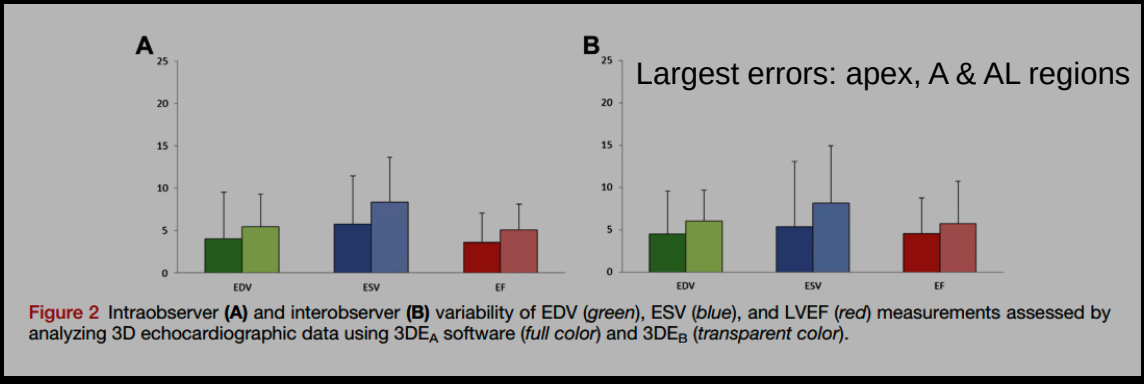


Figure 2 Intraobserver **(A)** and interobserver **(B)** variability of EDV (*green*), ESV (*blue*), and LVEF (*red*) measurements assessed by analyzing 3D echocardiographic data using $3DE_A$ software (*full color*) and $3DE_B$ (*transparent color*).

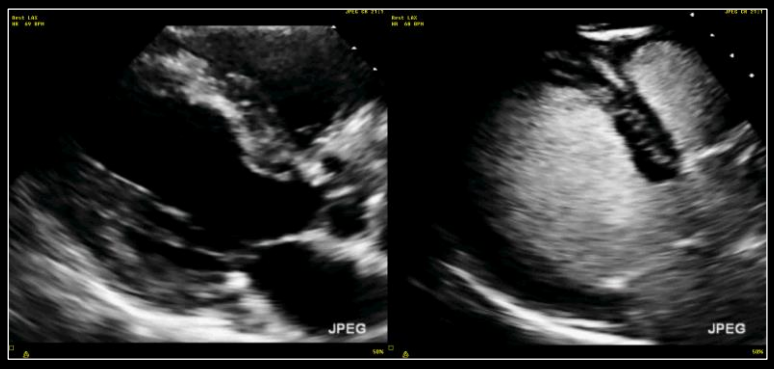
LVEF variability by 3DE: confounding factor for CTRCD dx

- *Different software should not be interchanged*
- *GLS: offers predictive value for subsequent cardiotoxicity*

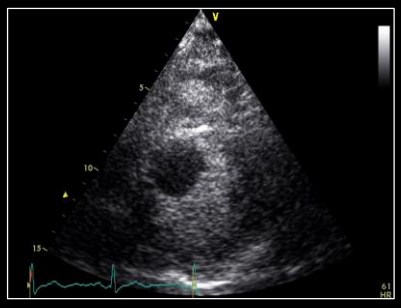
KEY POINT #6 - contrast

- UCA is useful for endocardial dropout
- Recommended when **two contiguous** LV segments are not well visualized on apical images
- Contrast agents are **not recommended** with 3DE in the serial follow-up of patients with cancer

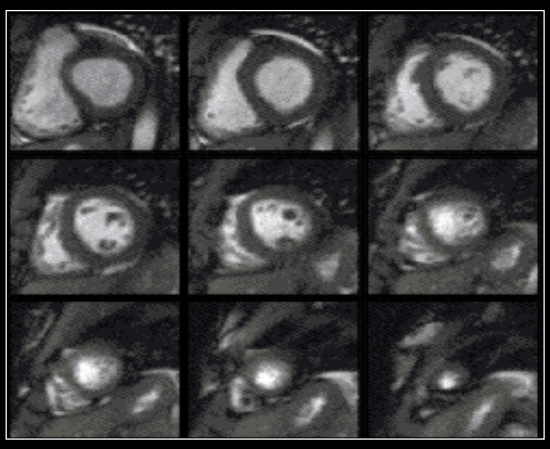
Contrast



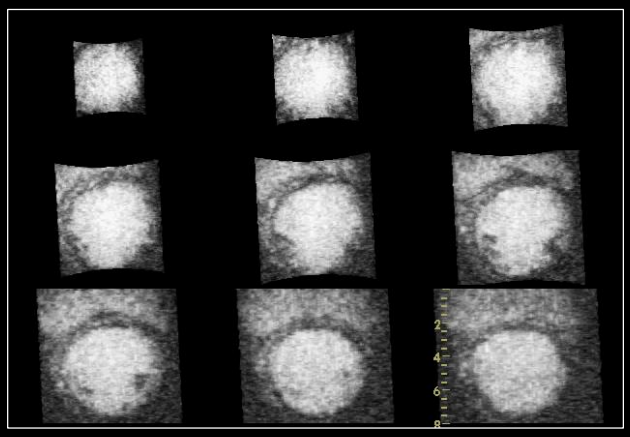
Impacts LV WT and LVd



Lights off…
Lights on…



Cardiac MRI (SAX stack)



Echo I-slice (SAX stack)

KEY POINT #7 – Stress echo

- Stress echo may help evaluate pts with IM / high pretest prob for CAD receiving Rx that cause ischemia (*fluorouracil, bevacizumab, sorafenib, sunitinib*)
- Stress echo may help determine *contractile reserve* of patients with CTRCD

KEY POINT #8 - Strain

- Strain should be measured with 2D STE > DTI
- GLS preferred to *detect subclinical LV dysfunction*
- Measures during chemo should be directly side-by-side compared with baseline value
  - Relative % reduction GLS **<8%** not meaningful (-20.0 > -18.4)
  - Relative % **>15%** very likely to be abnormal (-20.0 > -17.0)
  - No baseline exam, **< -19%** predicts later CTRCD
- For STE, use the same US machine

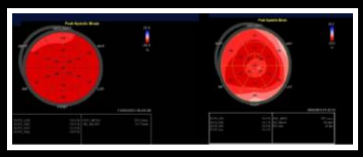
SPECKLE TRACKING

- There are *> 20 peer-reviewed reports* on deformation indices in detection of *subclinical cardiotoxicity* in pts treated for cancer
- Decrease in myocardial systolic function is rapid (within 2 hours of first dose) – 10-20%
  - This precedes reduced LVEF; or may occur without low LVEF
  - No preference to subendo, midmyo, or subepi (consistent with biopsy data of diffuse apoptosis)

Sawaya H, et al. Am J Cardiol 2011;107:1375-1380

SPECKLE TRACKING

GLS <16%



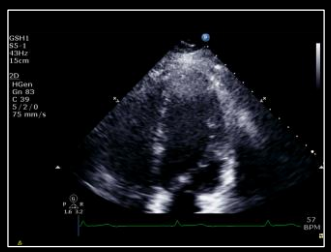
- Meta-Analysis: 24 articles
  - Normal GLS -15.9% to -22.1% (mean -19.7%)
- There were NO normal patients with GLS <15.9%

It is now recommended to give preference for GLS when a discrepancy exists between LVEF

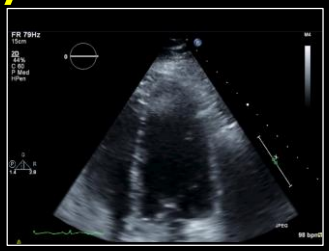
Yingchoncharoen T, Agarwal S, Popovic ZB, Marwick TH. JASE 2013;26:185-191

PATIENT CASE - EF

40F with multiple cycles of chemoRx

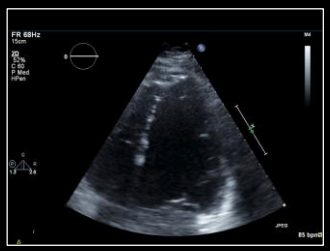


55%
February

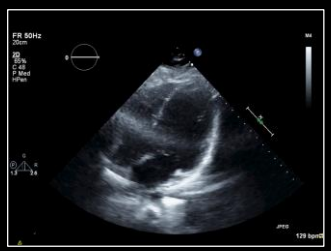


55% ~SOA
April

50% SOA
May



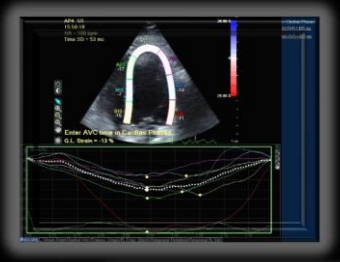
25% CHF
August



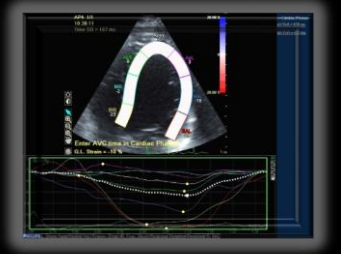
PATIENT CASE - GLS

40F with multiple cycles of chemoRx

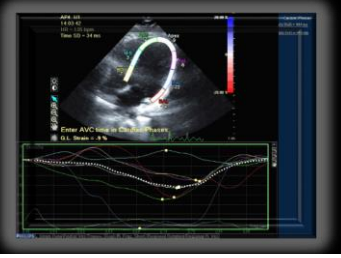
-19%
February



-16% ~SOA
April



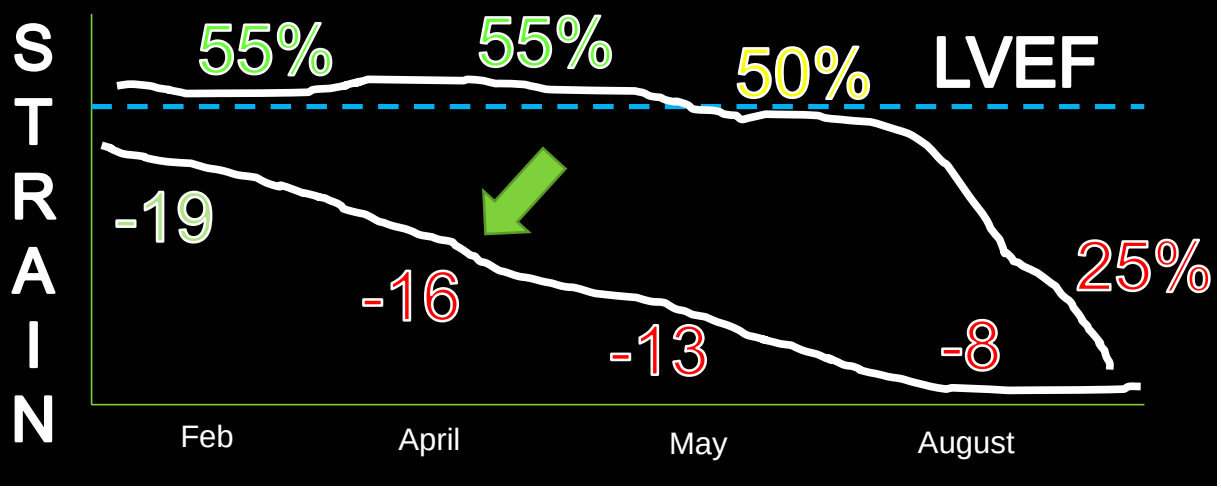
-13% SOA
May



-8% CHF
August

PATIENT CASE

40F with multiple cycles of chemoRx



Hot off the presses…

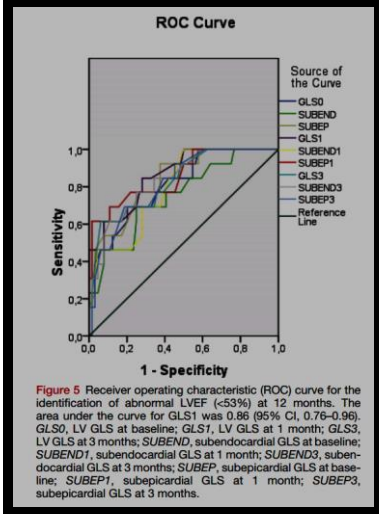


Figure 5 Receiver operating characteristic (ROC) curve for the identification of abnormal LVEF (<53%) at 12 months. The area under the curve for GLS1 was 0.86 (95% CI, 0.76–0.96). *GLS0*, LV GLS at baseline; *GLS1*, LV GLS at 1 month; *GLS3*, LV GLS at 3 months; *SUBEND*, subendocardial GLS at baseline; *SUBEND1*, subendocardial GLS at 1 month; *SUBEND3*, subendocardial GLS at 3 months; *SUBEP*, subepicardial GLS at baseline; *SUBEP1*, subepicardial GLS at 1 month; *SUBEP3*, subepicardial GLS at 3 months.

Following chemotherapy for BMT:
Myocardial deformation analysis detects subclinical bi-V dys
- 1 month after BMT, mainly subendocardial layer
- 3 months, subepicardial layer and LV twist are impaired

Suggests progressive subclinical cardiac dysfunction that precedes small reductions in LVEF

Abn GLS at 1 month predicts low LVEF at follow-up

http://dx.doi.org/10.1016/j.echo.2017.07.010

KEY POINT #9 - Troponin

- Elevated troponin may be a sensitive measure for *early detection* of CTRCD
- Natriuretic peptides, a marker of elevated filling pressures, are *less consistent* markers of early CTRCD

TROPONIN *cardiac biomarkers*

- Troponin: gold standard for *myocardial injury*
  - Predicts development of LV dysfunction after chemo
- N = 703; TnI each cycle (b/l, 12,24,36,72hrs; 1mo)
- **106/111 adverse CV events** in TnI elevation groups
  - 37% early (<72hrs) and 84% late (1month)
  - PPV 84%; NPV 99% (*identifies low risk pts*)

Note: "persistent" worse than "transient" TnI increase values

Cardinale D, et al. Circulation 2004;109:2749-20 2754

KEY POINT #10 - MUGA

- LVEF by MUGA is *highly reproducible*
- Main limitations are radiation, lack of ability to report on pericardium, valves, and RV

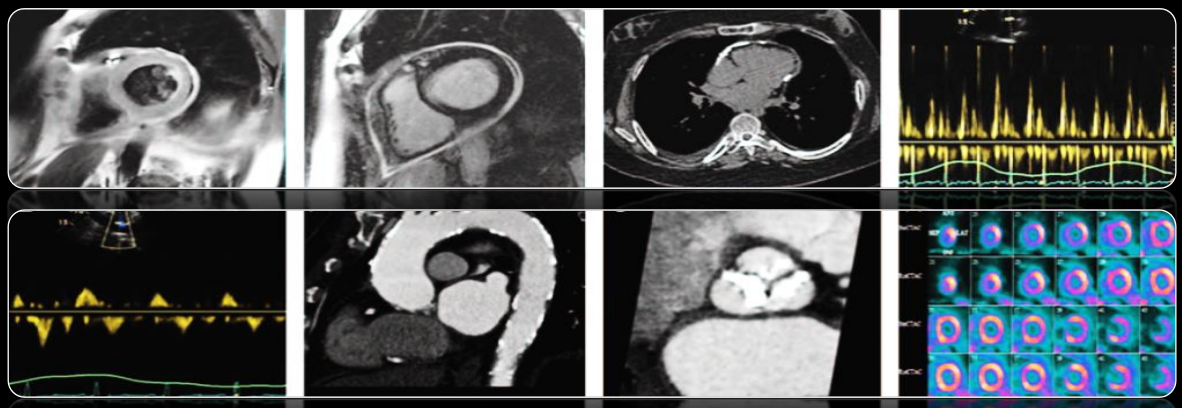
RADIATION THERAPY

- Radiation exposure to the thorax (Hodgkins, L>R breast)
  - Effective; used in >50% of cancer patients
    - High doses, younger age, coexistent CV risks
- Creating a growing population of CV dz

Pericardium	Coronaries
Vasculopathy	VHD
Cardiomyopathy	Conduction diseases

Cutter DJ, et al. Risks of heart disease after radiotherapy. Tex Heart Inst J 2011;38:257–258.

RADIATION THERAPY



52M; 18yrs post XRT

CONCLUSIONS

- Multi-specialty cooperation
- Oncologists make final call with Cardiology input
- XRT results in ~20 year delayed Ca++ presentations
- Definition of CTRCD is now defined
  - LVEF fall 10%, <53%, repeat imaging within 3 wks
- 3D Full Volume = guideline recommended
- Global Longitudinal Strain = guideline recommended

EXTRA MATERIAL

HIGH RISK PATIENTS

- Who should be screened by cardiology?
  - QUESTION? All pts versus high risk population?
  - Risk: age >65, HBP, DM, CAD, low / low normal EF, early decline, pt planning high dose (>350) or combined Rx
    - Consider cardio-protective therapies
- Should TnI be considered another guide?
- N = 413; Type I Rx; N = 114 (24%) with TnI +
  - Randomized to ACEi Rx (<1 mo after Rx) versus no Rx
  - LV size, LVEF, events (2% vs 52%) were improved

Cardinale D, et al. Circulation 2006;114:2474-2481

INTEGRATED APPROACH

- Integrated approach combines modern imaging with biomarkers for optimal subclinical detection and early preventive Rx
  - Used in “series”: reduction in frequency of imaging
  - Used in “parallel”: strategy for enhanced surveillance
- GLS <-19% or TnI + 93% specific for CTRCD
  - Versus 73% either parameter alone
  - Sensitivity 87% compared to 48% or 74% individually

Sawaya H, et al. Circ Cardiovasc Imaging 2012;5:596-603

PUTTING IT ALL TOGETHER

- Close corroboration between Onco, Card, and IM
- Baseline evaluation in all preferred; high risk in min
- This should include ECHO
  - Echo should include 3D and GLS / GCS; RWMA; contrast?
  - If images suboptimal (or borderline), perform CMR
- LVEF <50% or GLS <16% or TnI + … CARD CONSULT
  - Strongly consider cardioprotective Rx

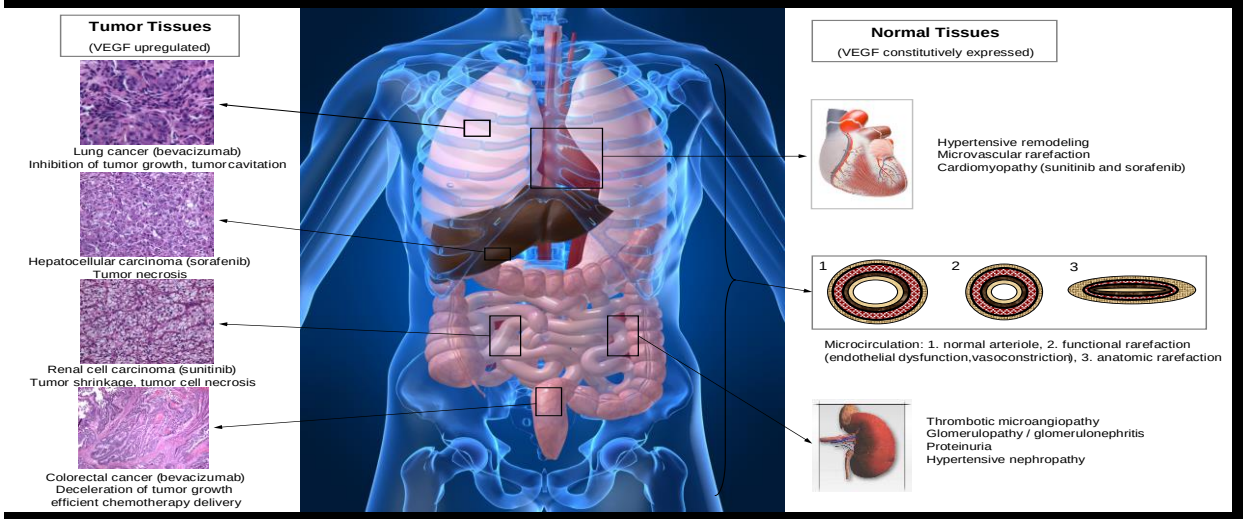
Sawaya H, et al. Circ Cardiovasc Imaging 2012;5:596-603

Table #1. Characteristics of Type I and II Chemotherapy-Related Cardiac Dysfunction

	Type I myocardial damage	Type II myocardial damage
Characteristic agent	Doxorubicin	Trastuzumab
Clinical course and typical response to anti-remodeling therapy (BB, ACE-I)	May stabilize, but underlying damage appears to be permanent and irreversible; recurrence in months or years may be related to sequential cardiac stress	High likelihood of recovery (to or near baseline cardiac status) in 2-4 months after interruption (reversible)
Dose effects	Cumulative, dose related	Not dose related
Effect of re-challenge	High probability of recurrent dysfunction that is progressive; may result in intractable heart failure or death	Increasing evidence for the relative safety of re-challenge (additional data needed)
Ultrastructure	Vacuoles; myofibrillar disarray and dropout; necrosis (changes resolve over time)	No apparent ultrastructural abnormalities (though not thoroughly studied)

Abbreviation: CRCD, chemotherapy-related cardiac dysfunction.

Systemic Effects of Anti-VEGF Therapy



Appendix # 1. Recommended Cardio-Oncology Echo Protocol

Standard Transthoracic Echo
- In accordance with ASE/EAE guidelines and ICAEL

2D Strain Imaging Acquisition
- Apical 4, 2, 3 chamber views
  * Acquire at least 3 cardiac cycles
- Images obtained simultaneously maintaining the same 2D frame rate and imaging depth
  * FPS between 40 – 90 or at least 40% of HR
- Aortic VTI (aortic ejection time)

2D Strain Imaging Analysis
- Quantify segmental and global strain (GLS)
- Display the segmental strain curves from apical views in a quad format
- Display the global strain in a bulls eyes plot

2D Strain Imaging Pitfalls
- Ectopy
- Breathing Translation

3D Imaging Acquisition
- Apical 4 chamber full volume to assess LV volumes and EF calculations
- Single and multibeats optimizing spatial and temporal resolution

Reporting
- 2D Biplane Simpson's method/3D EF
- GLS

RADIATION THERAPY

X-ray induced DNA breaks = apoptosis

Radiation-Induced Cardiovascular Injury

Risk factors
- Higher radiation doses
- Minimal or no cardiac protection techniques at time of irradiation
- Cardiac volume exposed to irradiation
- Young age at irradiation
- Increasing interval from time of radiation
- Pre-existing cardiovascular risk factors

Acute Cardiac Injury
(less common)
Acute pericarditis
Myocarditis

Late Cardiac Injury
Constrictive pericarditis
Restrictive cardiomyopathy
Coronary artery disease
Valvular disease
Conduction disturbances

Medium or Large Vessel Vasculopathy
Thoracic aortic calcification (porcelain aorta)
Carotid/axillary/subclavian artery stenosis

Groarke JD, et al. CV complications of radiation therapy… Eur Heart J. 2013

RADIATION THERAPY

- Thoracic: suspect *cardiac* injury
  - CAD: Sx-guided (ACS – invasive / non-ACS – functional)
    - Asymptomatic: CCTA, CACS (or functional) 5yrs post XRT
  - Pericardium: Sx-guided only (TTE +/- CMR or CCT)
  - **VHD: Routine TTE 10yrs post-XRT (sooner if Sx)**
- Head and Neck: suspect *arterial* disease
  - CVA Sx or carotid bruit: Carotid US +/- MRA/CTA
  - No Sx but PAD and/or RF's AND 10yrs post: US +/- MR/CT
- ALL: **CT chest PRIOR to CT surgery** (guide surgical risk: *mediastinal fibrosis, porcelain Ao*)

CTRCD Guidelines

- EMB used for Dx 1970's (replaced by serial LVEF)
  - Variable: LVEF measures / onset of dysfunction / cardiac reserve
- Diagnosis: >10% fall in LVEF to <53% on 2 serial echo's
  - Subcategorized as Reversible, Partially reversible, Irreversible
- Type of Injury: Type I vs Type II CTRCD
  - Randomized to ACEi Rx (<1 mo after Rx) versus no Rx
  - LV size, LVEF, events (2% vs 52%) were improved

Table 1 Characteristics of type I and II CTRCD

	Type I	Type II
Characteristic agent	Doxorubicin	Trastuzumab
Clinical course and typical response to antiremodeling therapy (β-blockers, ACE inhibitors)	May stabilize, but underlying damage appears to be permanent and irreversible; recurrence in months or years may be related to sequential cardiac stress	High likelihood of recovery (to or near baseline cardiac status) in 2–4 months after interruption (reversible)
Dose effects	Cumulative, dose related	Not dose related
Effect of rechallenge	High probability of recurrent dysfunction that is progressive; may result in intractable heart failure or death	Increasing evidence for the relative safety of rechallenge (additional data needed)
Ultrastructure	Vacuoles; myofibrillar disarray and dropout; necrosis (changes resolve over time)	No apparent ultra structural abnormalities (though not thoroughly studied)

Change in EF

Type of Toxicity

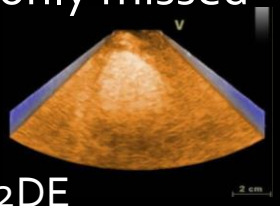
DEFINITION CTRCD

Symptoms

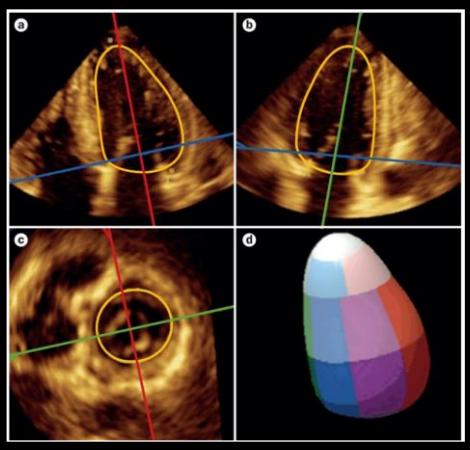
Reversibility

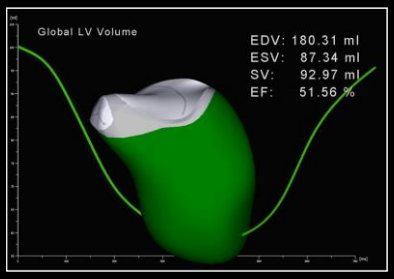
ECHO Modalities

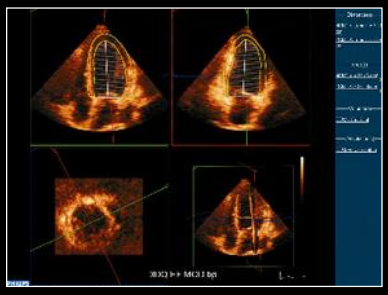
- LVEF using biplane Simpson or 3DE
  - Use contrast as needed (? 2 segments apical views)
- Include WMSI since subtle WMA commonly missed on routine 2DE
- 3DE: *better accuracy for LVEF <50%*
  - Better reproducibility / lower variability vs 2DE
  - Do not combine with contrast (basal drop out limits use)



Sorrell VL, Nanda NC. Atlas of 3D Echocardiography. 2007







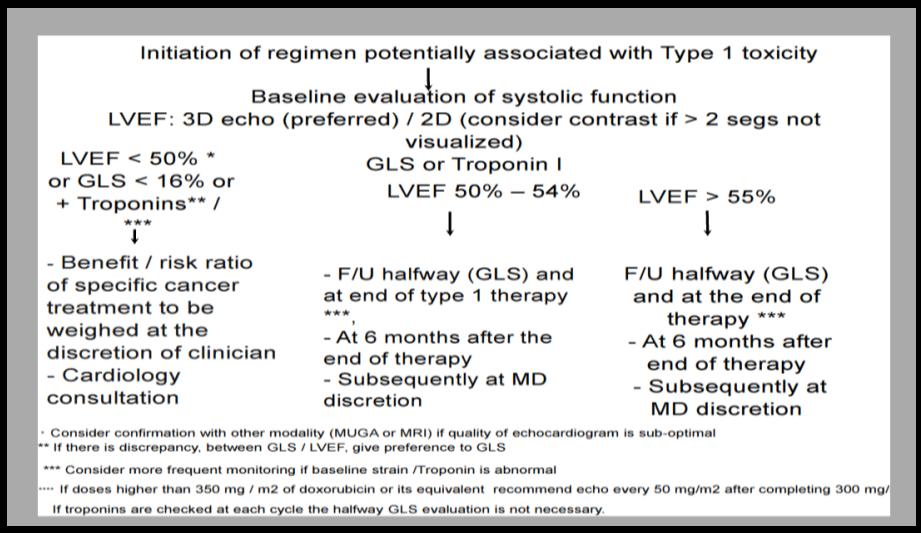
Subclinical LVD

- Imaging:
  - LVEF 50-54%: increased cardiac event rates
  - *Despite DDfx preceding LVd*, evidence DOES NOT support DDfx indices for prediction of CTRCD
  - STRAIN (myo deformation): STE preferred > DTI
  - *GLS best predictor of early CTRCD* (compared serially)
    - <8% reduction is NOT considered clinically meaningful

DEFORMATION IMAGING

- N=81; breast cancer; Type I and II agents
- Follow up: 15 months; quarterly echo's
- Post-Rx GLS predicted 100% heart failure (all <-19%)
  - Also predicted LVEF <55% or decrease >10% at f/u
  - Unknown if this persists longer
- GLS was predictive, but GCS and radial strain wasn't
  - Radial strain – not sensitive enough (fractional thickening)
  - GCS is a compensatory mechanism for impaired GLS

Sawaya H, et al. Circ Imaging 2012;5:596-603



Cardiac monitoring in patient receiving type 1 regimen

- CHF
- Confirmed drop of 10 points to LVEF < 50% (*)
- GLS < 16%.

↓

- Cancer treatment at discretion of clinician
- Cardiology consultation

- Asymptomatic drop of 10 points to LVEF 50 – 54% **
- Relative drop GLS >15% as compared to baseline
- + troponin

↓

Sub-clinical LV dysfunction

- LVEF > 55%
- GLS > 19%
- Relative drop of GLS of <8% as compared to baseline
- - Troponins

↓

No evidence of sub-clinical LV dysfunction.

* Consider confirmation with other modality3D / MRI / MUGA.

Initiation of trastuzumab

↓

Baseline evaluation of systolic function
LVEF: 3D (preferred)/ 2D (consider contrast)
GLS, Troponin I

LVEF < 50%*	LVEF 50-54%	LVEF > 55%
- Cancer treatment at discretion of clinician - Cardiology consultation - Follow up with LVEF/GLS/ before each trastuzumab treatment, or troponin after, then at 6 months of follow up.	- Follow up every 3 months with LVEF /GLS during therapy. and then at MD discretion - If GLS<19 consider increased echo frequency and measure troponins	- Follow up every 3 months with LVEF /GLS during therapy. - If GLS < 19,consider increased echo frequency and measure troponins

* Consider confirmation by 3D /MUGA/MRI

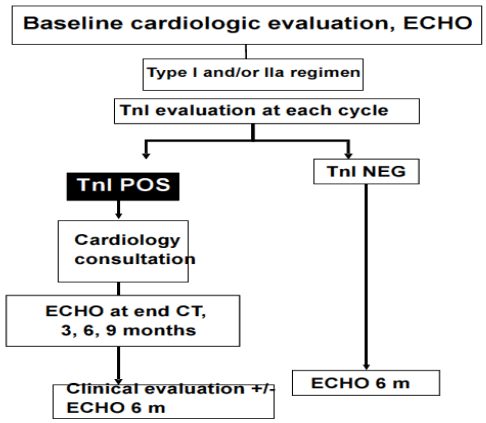
Initiation of trastuzumab after regimen associated with Type 1 toxicity

Baseline evaluation of systolic function
LVEF: 3D (preferred)/ 2D (consider contrast)
GLS, Troponin I

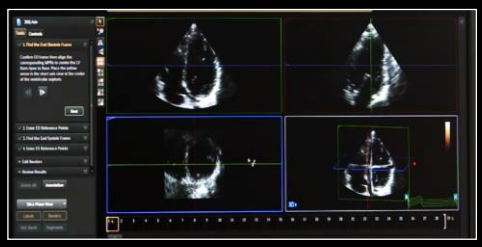
-LVEF < 50%* - GLS <16%	- EF 50-54% - + Tn I	- LVEF 55% - GLS>19% - Tn I
- Trastuzumab at discretion of clinician - Cardiology consultation	- Consider Cardiology consultation - F/U every 3 months during therapy. -F/U up at 6 months after completion of therapy an then at MD discretion.	- F/U every 3 months during therapy -F/U at 6 months after end of therapy and then at MD discretion.

* Consider confirmation by 3D /MUGA/MRI
** Consider more frequent monitoring if dose >300mg/m2

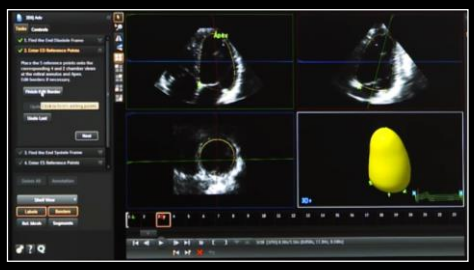
Early detection of toxicity using biomarkers

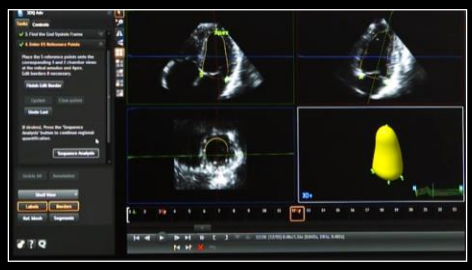


Modified from Curigliano G et al. Ann Oncol 2012

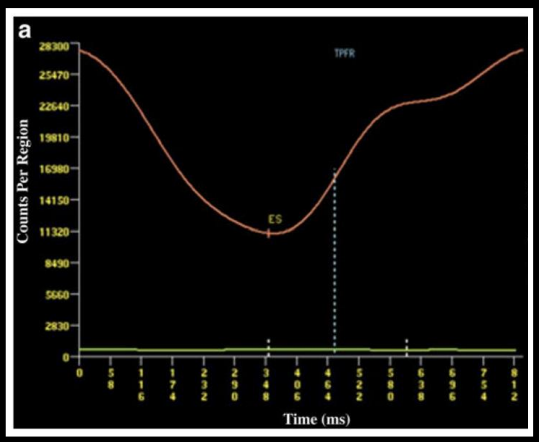


3DE





Nuclear – MUGA / eRNA



Future Imaging

- ^{123}I-mIBG - Sympathetic neuronal imaging
- ^{111}In-antimyosin – myocyte necrosis
- 99m Tc-annexin V – marker of apoptosis
- ^{111}In-traxtuzumab – HER2/neu receptor marker

Potential methods to identify pre-clinical cardiotoxicity and monitor Rx directed at reducing apoptosis