How I Use Strain in Everyday Cardio Oncology Practice

Echo Hawaii
January 17, 2022

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Disclosures

Consultancy Fees: Caption Health, Pfizer, Philips

DSMB: Caelum

Grant support: Johnson and Johnson

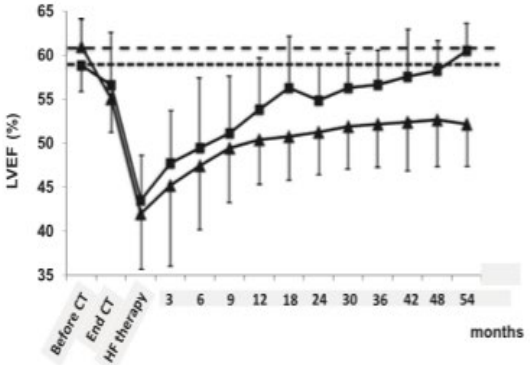
Why use strain in cardio-oncology

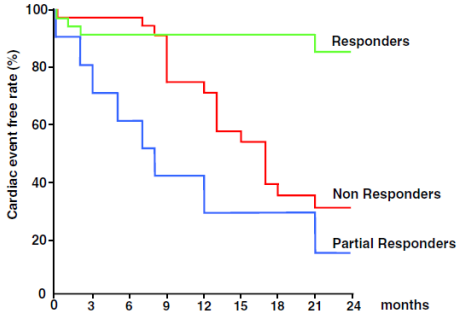
- Sensitive and reliable measure of LV systolic function
- An early marker of cardiotoxicity
- Risk stratification; identifying high-risk patients
- Guide cardioprotective management

Cardiac Monitoring: 2D Echo

- Most used method world-wide for monitoring chemotherapy related cardiotoxicity
- Feasible, safe and low cost
- Able to assess more than ventricular function
- Lack of radiation exposure
- LVEF is the most used parameter to assess cardiotoxicity

Early detection of cancer therapy related cardiac dysfunction (CTRCD): Is 2D LVEF enough?





- 2,635 pts receiving anthracycline based tx
- EF q3 months during tx, then 6 months post tx for 4 years
- HF medication initiated when cardiotoxicity detected (LVEF decrease > 10% and <50%)
- LVEF improvement in 82%
  - 11% total recovery
  - 71% partial recovery
  - 18% no recovery
- Pts with no recovery had higher incidence of adverse cardiac events (death, acute pulmonary edema, HF hospitalization, life threatening arrhythmia, conduction abnormalities requiring PM)

EF decline, a late phenomenon, sufficient myocardium damaged to allow complete LV recovery.

MORE SENSITIVE INDICES NEEDED!

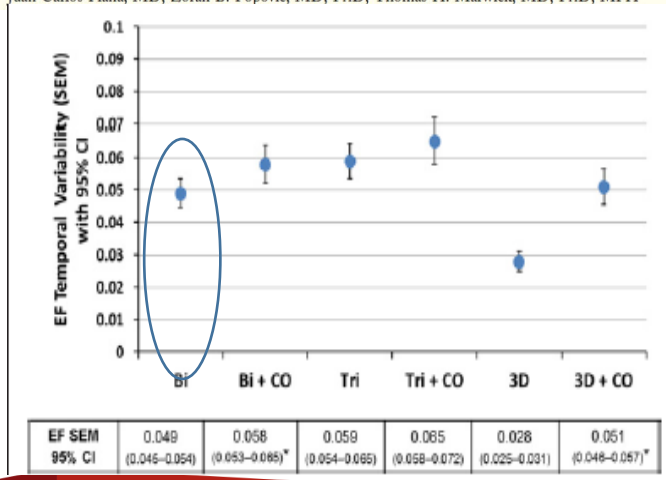
Cardinale D, Circulation 2015;131:1981-8

Is 2D LVEF enough?
2D LVEF Limitation: Reproducibility

Reproducibility of Echocardiographic Techniques for Sequential Assessment of Left Ventricular Ejection Fraction and Volumes

Application to Patients Undergoing Cancer Chemotherapy

Paaladinesh Thavendiranathan, MD, MSc, Andrew D. Grant, MD, Tomoko Negishi, MD, Juan Carlos Plana, MD, Zoran B. Popović, MD, PhD, Thomas H. Marwick, MD, PhD, MPH



	Bi	Bi + CO	Tri	Tri + CO	3D	3D + CO
EF SEM 95% CI	0.049 (0.046–0.054)	0.058 (0.053–0.065)*	0.059 (0.054–0.065)	0.065 (0.058–0.072)	0.028 (0.025–0.031)	0.051 (0.048–0.057)*

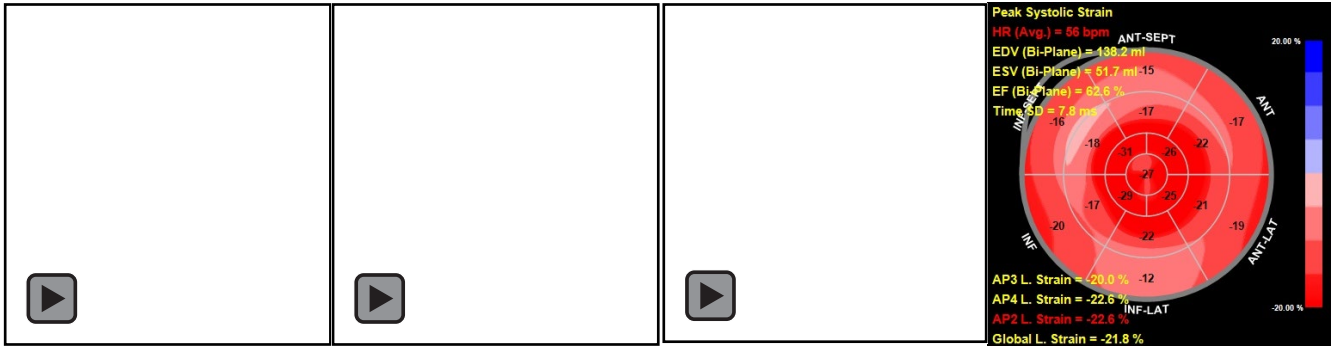
2D EF: minimal detectable difference 10%

Definition of Cardiotoxicity (CREC):

- ❑Asymptomatic reduction of the LVEF of ≥10% to <55%
- ❑Reduction of LV EF of ≥ 5% to <55% with symptoms of heart failure

Thavendiranathan P. et al. J Am Coll Cardiol 2013;61:77-84
Seidman A, et al J Cin Oncol 2002; 20:1215-1221

Global Longitudinal Strain (GLS): An Index of Longitudinal Myocardial Shortening



- Most commonly used in clinical practice
- Most robust in terms of reproducibility
- Sensitive for assessing myocardial function and detection of subclinical LV dysfunction
- Superior to 2D EF in:
  - Reproducibility (10% EF vs <1.7% GLS absolute error)
  - Correlation with MRI-EF
  - Prediction of overall outcome

Brown et al, Am Heart J 2009;157(1)
Stanton et al, Circ CV Imaging 2009;2(5)
Farsalinos et al, JASE 2015;28:1171-81

GLS in Cardio-Oncology: Why the buzz?

Strain changes before EF changes

Early Marker of Cardiotoxicity!

Global Longitudinal Strain: Early Biomarker for Cardiotoxicity

ASE American Society of Echocardiography
Sound Saves Lives

Reduction in GLS Predicts ↓ in LVEF

Journal of the American College of Cardiology
© 2014 by the American College of Cardiology Foundation
Published by Elsevier Inc.
Vol. 63, No. 25, 2014
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2014.01.073

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,*
Juan Carlos Plana, MD,‡ Anna Woo, MD,* Thomas H. Marwick, MD§
Toronto, Ontario, Canada; Cleveland, Ohio; and Hobart, Australia

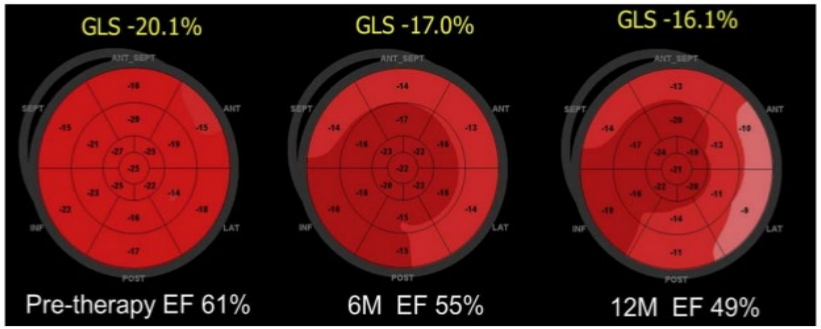
JAMA Cardiology | Original Investigation

Assessment of Prognostic Value of Left Ventricular Global Longitudinal Strain for Early Prediction of Chemotherapy-Induced Cardiotoxicity

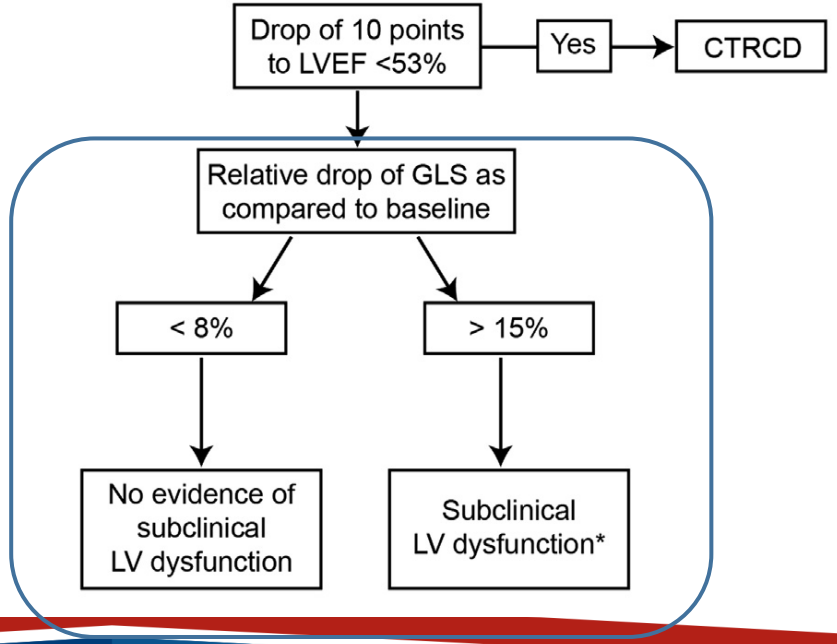
A Systematic Review and Meta-analysis

August 2019

Evangelos K. Oikonomou, MD; Damianos G. Kokkinidis, MD, MSc; Polydoros N. Kampaktsis, MD; Eitan A. Amir, MD, PhD; Thomas H. Marwick, MD, PhD, MPH; Dipti Gupta, MD, MPH; Paaladinesh Thavendiranathan, MD, MSc



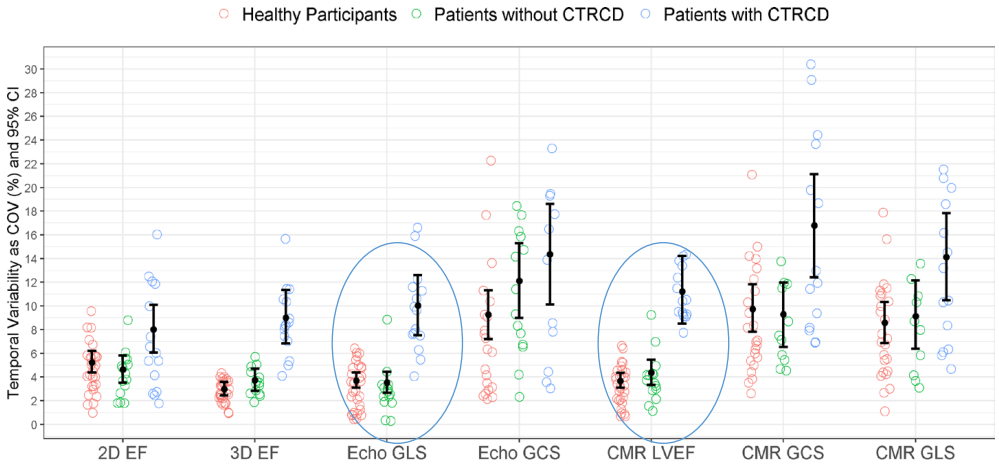
Expert Consensus for Multimodality Imaging Evaluation of Adult Patients during and after Cancer Therapy: A Report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging



Plana J et al JASE 2014;27:911-39

GLS: Reproducibility

cMRI and Echo LVEF and strain for detection of CTRCD



	2D EF	3D EF	Echo GLS	Echo GCS	CMR LVEF	CMR GCS	CMR GLS
Healthy Participants	5.2 [4.4, 6.2]	3.0 [2.5, 3.6]	3.7 [3.1, 4.4]	9.3 [7.2, 11.3]	3.7 [3.1, 4.3]	9.7 [7.8, 11.8]	8.6 [6.9, 10.3]
Patients without CTRCD	4.6 [3.5, 5.8]	3.8 [2.8, 4.7]	3.5 [2.7, 4.4]	12.1 [9.0, 15.3]	4.4 [3.3, 5.5]	9.3 [6.5, 12.0]	9.1 [6.4, 12.1]
Patients with CTRCD	8.0 [6.1, 10.1]	9.0 [6.8, 11.4]	10.0 [7.5, 12.6]	14.4 [10.1, 18.6]	11.2 [8.5, 14.2]	16.8 [12.4, 21.1]	14.1 [10.5, 17.8]

CMR-LVEF and echo GLS had the optimal temporal and observer variability

In the absence of CMR LVEF, echo GLS could be considered the method with least variability for monitoring myocardial functional changes in patients receiving cancer therapy

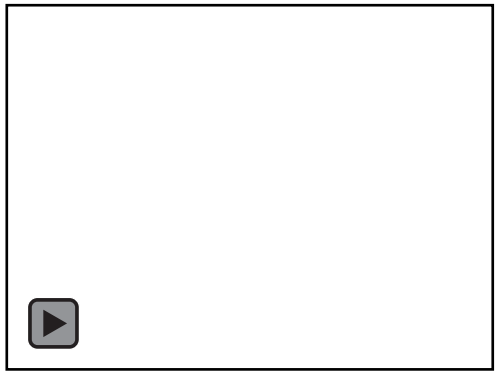
Lambert J, Thavendiranathan Heart 2020

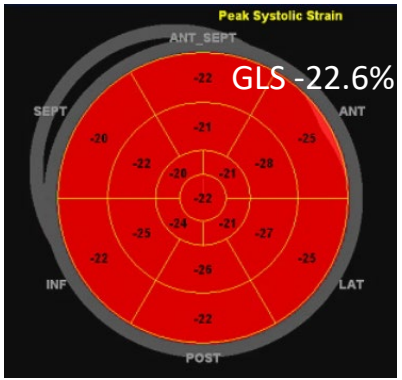
Case 1

57-year-old woman with locally advanced HER 2+ breast cancer

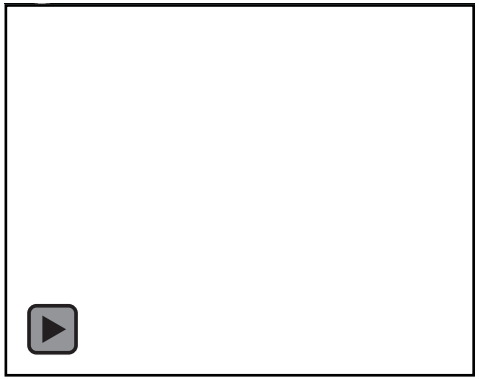
- PMH - DM, HTN on amlodipine/HCTZ. No prior cardiac history.
- s/p mastectomy, adjuvant anthracycline-based chemotherapy (doxorubicin, cyclophosphamide, taxol)
- Ready to start trastuzumab/pertuzumab + radiotherapy
- Asymptomatic w/o cardiac symptoms

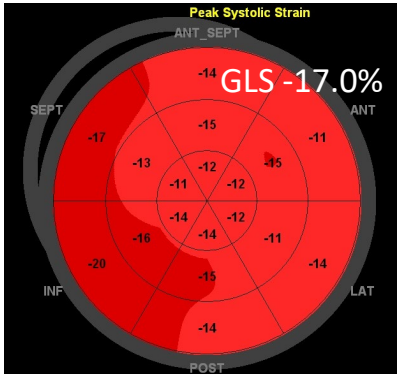
Follow-up Echo





Baseline
EF 67%; GLS 22.6%





Post Anthracycline
EF 59%; GLS 17%

Δ EF 8% from 67% to 59%;
Δ GLS 25% from 22.6% to 17%

∆ EF 8% from 67% to 59%;
∆ GLS 25% from 22.6% to 17%

What to do next?

A) **Nothing. The changes are not clinically meaningful as LVEF is still within normal range.**

B) **Stop further cancer treatment as GLS has dropped by 25%**

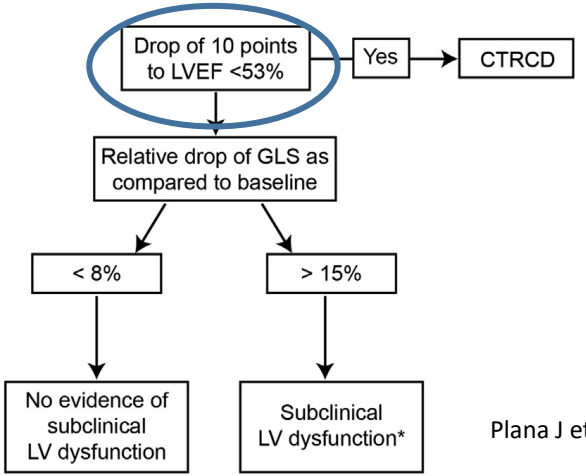
C) **Check cardiac biomarkers**

D) **Pt has developed subclinical cardiotoxicity. Optimize cardiac risk factors. Close surveillance.**

Asymptomatic Δ EF 8% from 67% to 59%
Criteria for CTRCD – YES or NO?

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



Plana J et al JASE 2014;27:911-39

Cardiac Review and Evaluation Committee/FDA

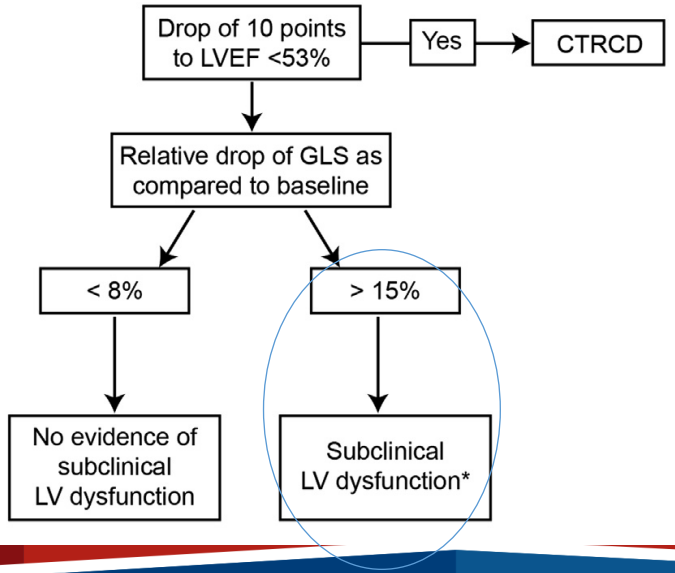
- Symptoms or signs associated with heart failure
- Asymptomatic reduction of LVEF of ≥10% to <55%
- Absolute decrease in LVEF ≥ 16% from pre-treatment level values.

Seidman A, JCO 2002;20(5):1215-21

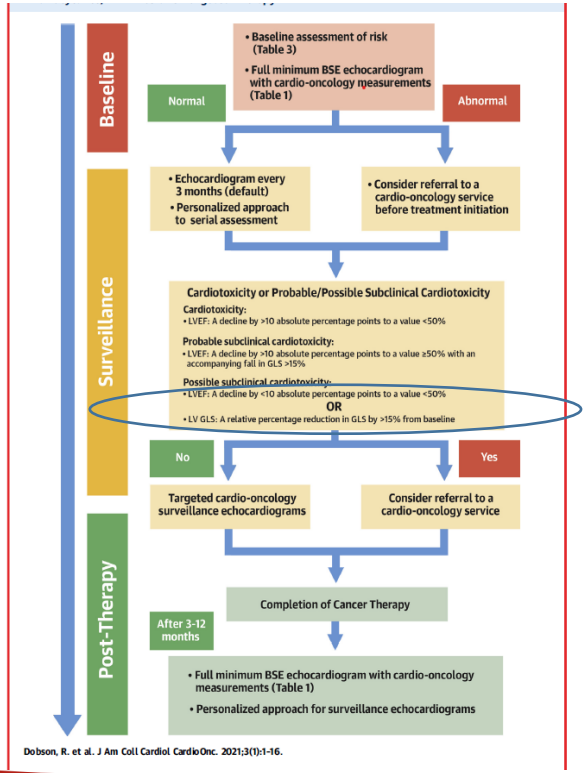
Case 1: Δ GLS 25% from 22.6% to 17%
Subclinical LV Dysfunction – YES or NO?

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

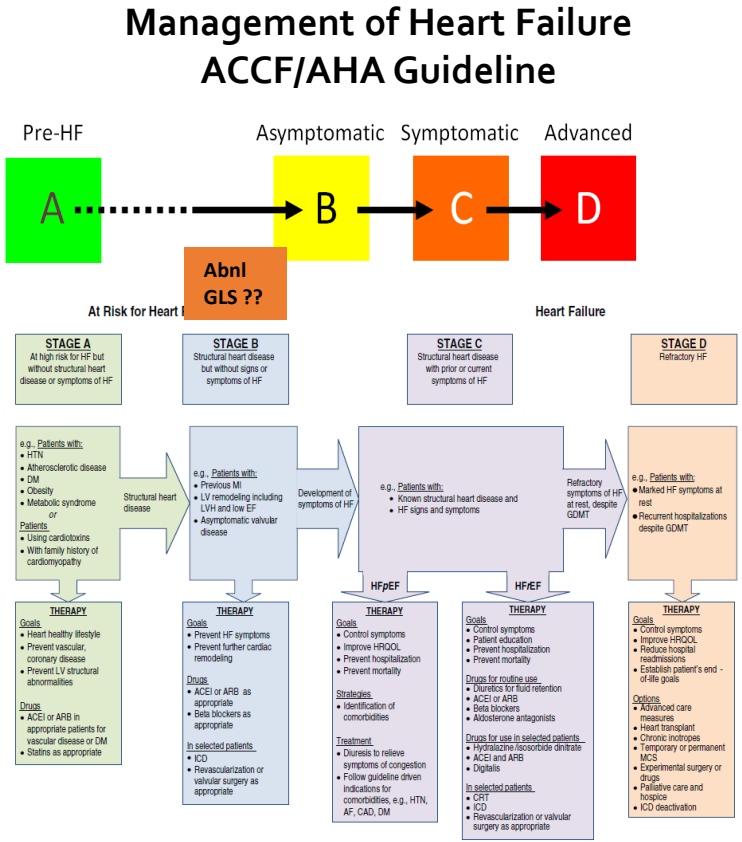


British Society Echo and British Cardio Oncology Guideline



Dobson, R. et al. J Am Coll Cardiol CardioOnc. 2021;3(1):1-16.

Clinical significance of subclinical LV dysfunction by GLS? Therapeutic Implications?



Strain Guided Response: SUCCOUR Study
Multicenter prospective randomized trial

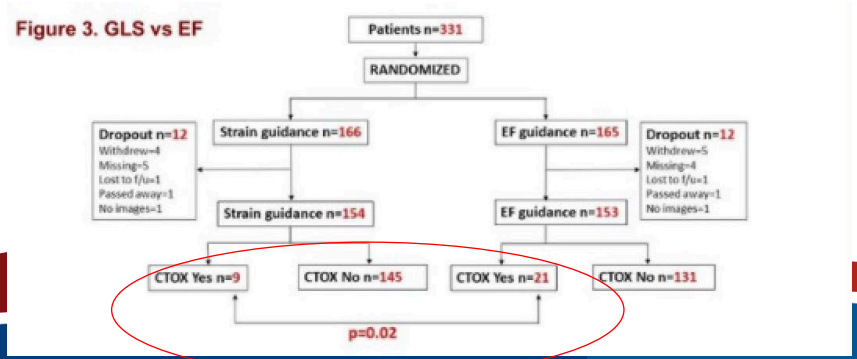
Hypothesis: Strain guided use of cardioprotective therapy (CPT) will limit the development of reduced LV EF.

1-year results of strain guided response

TABLE 2 Changes in LVEF and GLS Between Baseline and the 1-Year Follow-Up

	EF Guided			GLS Guided				
	n	LV Function, % (95% CI)	p Value*	n	LV Function, % (95% CI)	p Value*	Difference, % (95% CI)	p Value†
Core laboratory 3D EF, %								
Baseline	153	58 (57 to 59)		154	59 (58 to 60)		-1.2 (-2.6 to 0.2)	0.10
1 year	153	55 (54 to 56)		154	57 (56 to 58)		-1.5 (-3.0 to 0.0)	0.05
1 year – baseline	153	-3.0 (-1.8 to -4.2)	<0.001	154	-2.7 (-1.7 to -3.8)	<0.001	0.3 (-1.3 to 1.9)	0.69
Core laboratory GLS, %								
Baseline	153	-20.4 (-20.8 to -20.0)		154	-20.9 (-21.3, to -20.5)		0.49 (-0.05 to 1.03)	0.08
1 year	142	-19.0 (-19.5 to -18.6)		136	-19.6 (-20.0 to -19.2)		0.53 (-0.07 to 1.13)	0.08
1 year -baseline	142	1.5 (1.9 to 1.0)	<0.001	136	1.4 (1.8 to 1.0)	<0.001	-0.09 (-0.68 to 0.49)	0.75

Figure 3. GLS vs EF



- CPT: GLS dropped >12% in GLS guided arm; EF dropped >10% to less than 55% in both arms
- Primary outcome of change in LVEF not significantly different between the 2 arms (-3.0 vs. -2.7%).
- Less incidence of cardiotoxicity in GLS guided arm than the standard EF guided arm (9/166 vs. 21/165, p = 0.02)
- Concluded that results support the use of GLS in monitoring CTRCD

Thavendiranathan D et al JACC 2021;77:392-401

EDITORIAL COMMENT

Global Longitudinal Strain in Cardio-Oncology*

Javid J. Moslehi, MD,[a] Ronald M. Witteles, MD[b]

For which of my bad parts didst thou first fall in love with me?
—Much Ado About Nothing, William Shakespeare (1)

Key points:

- Failed to meet the primary endpoint with no difference in LVEF from baseline to 1 year in the two arms (-3.0% vs. -2.7%).
- No difference in the proportion of patients with LVEF <55% at 1 year between the two arms
- Conclusion: Study findings suggest a lack of efficacy for GLS in the assessment of cardiotoxicity

Secondary endpoint of cancer therapy related cardiac dysfunction (CTRCD) incidence - lower in the GLS guided arm (5.8%) than the LVEF guided arm (13.7%), deserves more discussion.

JACC 2021 Feb, 77 (4) 402–404

Clinical significance of asymptomatic LV dysfunction??

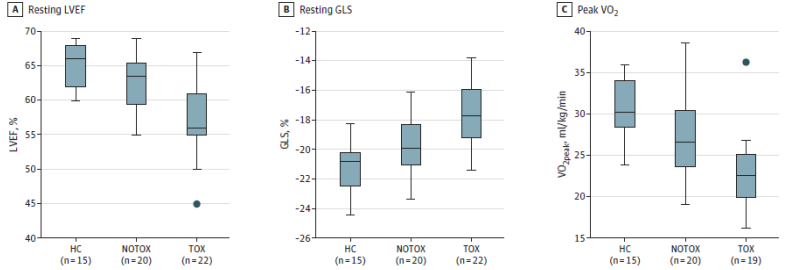
JAMA Cardiology | Original Investigation

Long-term Cardiopulmonary Consequences of Treatment-Induced Cardiotoxicity in Survivors of *ERBB2*-Positive Breast Cancer

Anthony F. Yu, MD; Jessica R. Flynn, BS; Chaya S. Moskowitz, PhD; Jessica M. Scott, PhD; Kevin C. Oeffinger, MD; Chau T. Dang, MD; Jennifer E. Liu, MD; Lee W. Jones, PhD; Richard M. Steingart, MD

JAMA Cardiol. 2020;5(3):309-31

Figure. Cardiopulmonary Function as Assessed by Resting Left Ventricular Ejection Fraction (LVEF), Resting Global Longitudinal Strain (GLS), and Peak Oxygen Consumption (Peak VO_2)



5+ year BC survivors with TOX vs. NOTOX

- Significantly lower peak VO2, LVEF and GLS.

TOX: asymptomatic decrease of LVEF> 10% from baseline to <55%

Long-term marked impairment of cardiopulmonary function is associated with CTRCD among survivors of breast cancer treated with trastuzumab based therapy

Case 1. GLS drop with preserved LVEF during treatment: Subclinical cardiotoxicity

Clinical Implications:

- Marker of increased risk, predictive of subsequent EF fall
- Closer surveillance for signs and symptoms of cardiac dysfunction
- Cardioprotective therapy to prevent LVEF decline may be beneficial
- Has not been shown to predict clinical heart failure or death

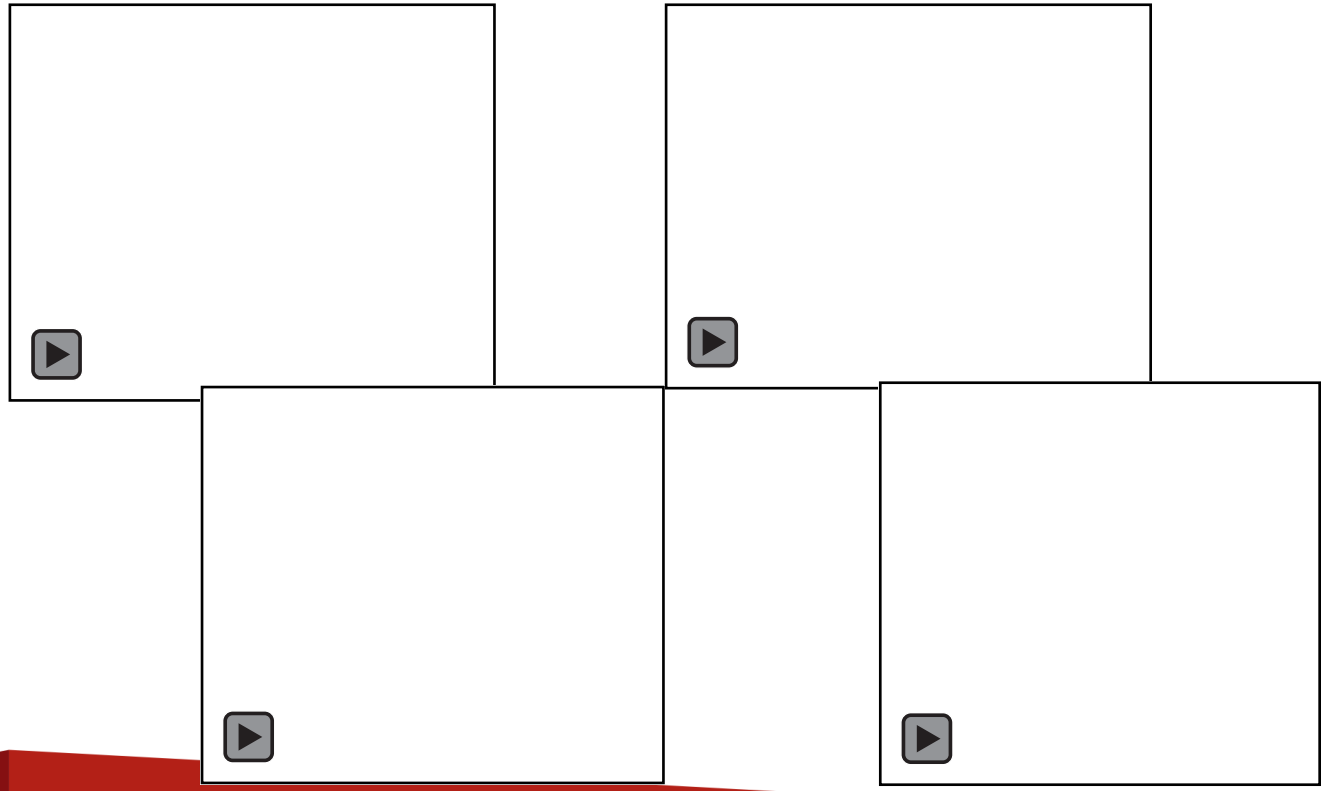
Case 1

57-year-old woman with locally advanced HER 2+ breast cancer with subclinical LV dysfunction (asymptomatic LVEF drop of 8% from 67% to 59% and relative GLS drop of 25% from 22.6% to 17%)

Recommendations:

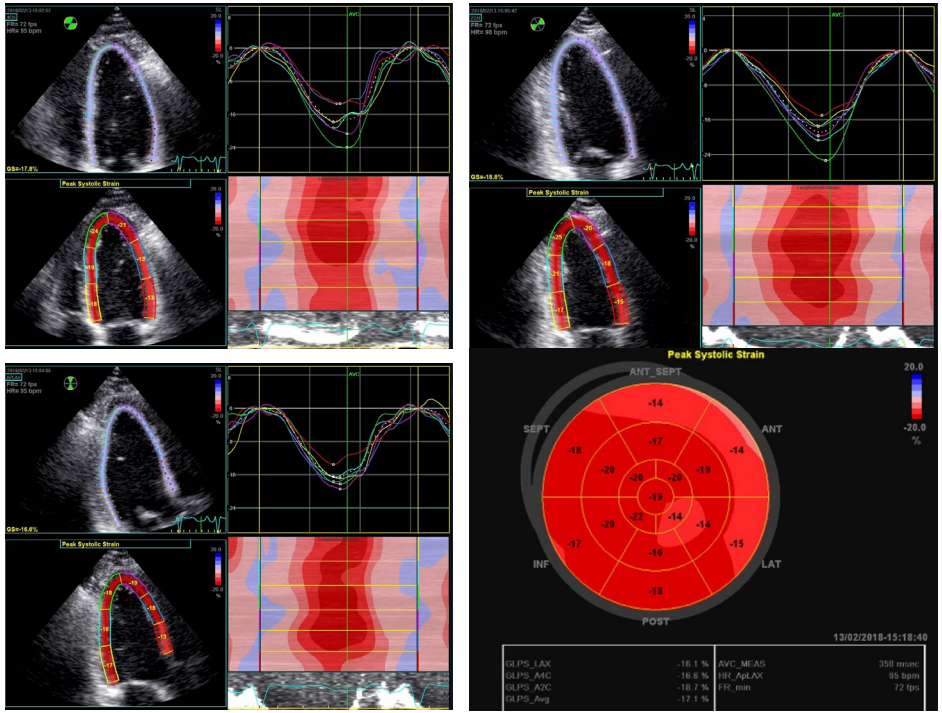
- Change anti-HTN from amlodipine/HCTZ to cardioprotective agents such as carvedilol and/or ACEI/ARB
- Initiate trastuzumab/pertuzumab + radiotherapy
- Close surveillance for signs and symptoms of cardiac dysfunction

Case 2: 40-year-old survivor of retinoblastoma diagnosed at infancy; prior 450 mg/m2 doxorubicin tx; now with metastatic breast cancer. Prior echo studies: EF range 45-60%. OK to initiate more anthracycline?



LVEF 55%

GLS = 17.1% ➡ Borderline Low



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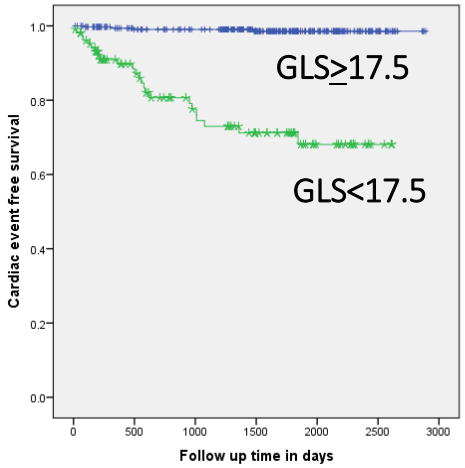
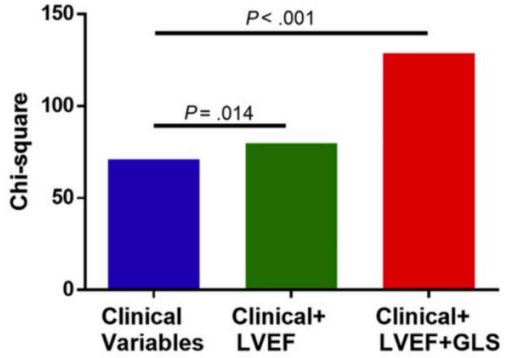
Prognostic Value of GLS Predictive of Risk

450 patients with hematological malignancies treated with anthracycline. Pre-treatment GLS:

- Identifying patients at higher risk for heart failure and cardiac death
- Provided incremental value over clinical variables and LVEF in identifying subsequent clinical HF and cardiac death

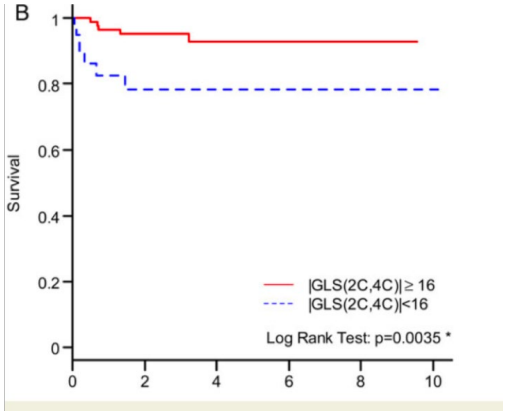


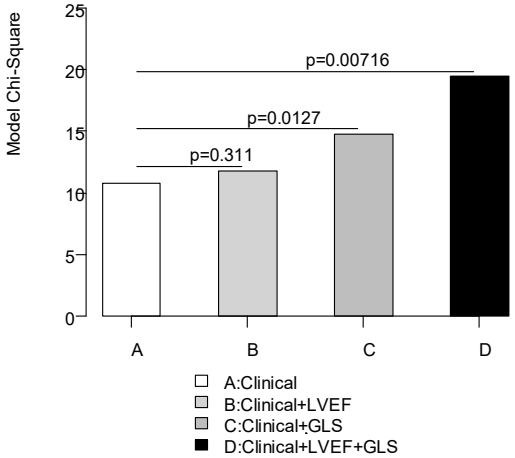


Ali M, Scherrier-Crosbie M, J Am Soc Echocardiogr 2016;29:522-527

Incremental Prognostic Value of GLS LVEF between 50-59%

- Retrospective study of 158 patients prior to tx with anthracycline
- Baseline GLS predictive of occurrence of subsequent symptomatic HF and overall mortality and provide incremental value beyond clinical risk factors and EF

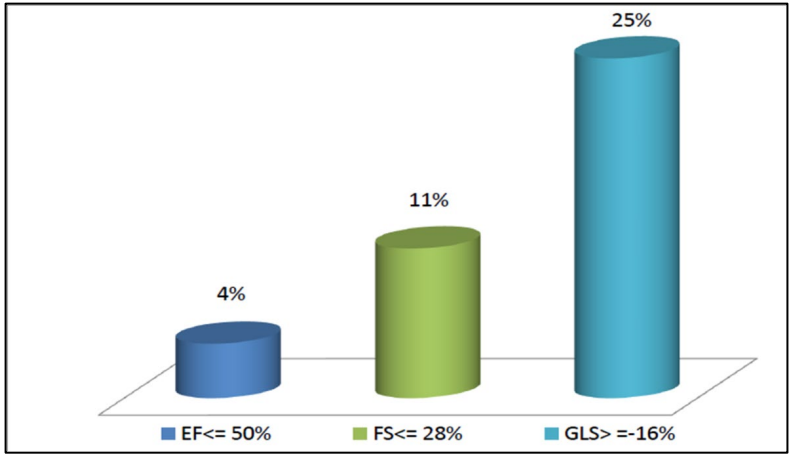




Mousavi N, Scherrer-Crosbie M, et al. Euro Heart J CV Imag 2015

Prevalence of LV Systolic Dysfunction in Long-Term Survivors of Childhood Cancer: 2D strain vs. EF

Cohort (N=134) of adult survivors (10+ years) of childhood cancer with anthracycline/RT exposure



* EF = Ejection Fraction, FS= Fractional Shortening, GLS= Global Longitudinal Strain

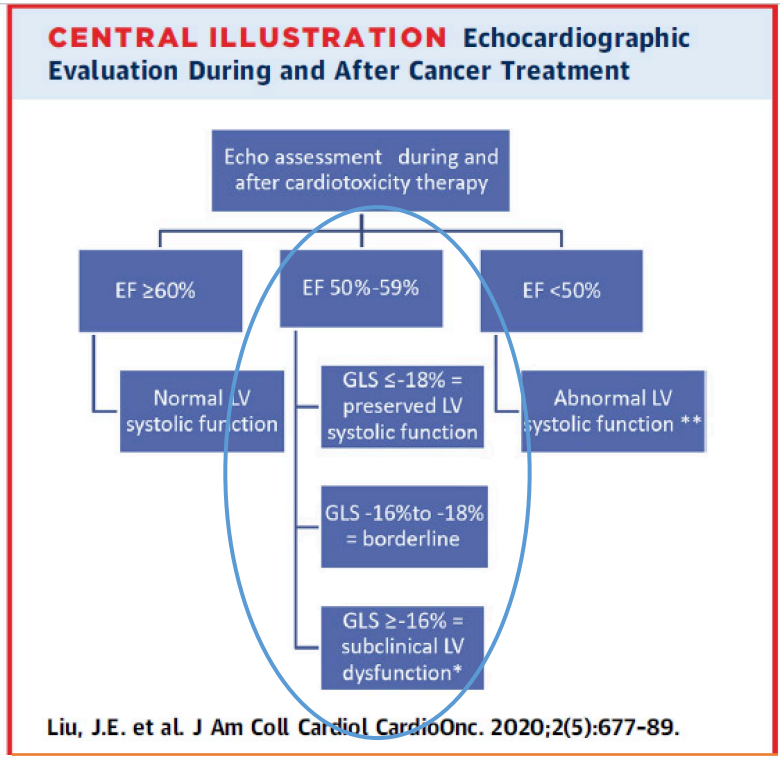
- 25% of the survivors had GLS <16% (2 SD below normal)
- Continued cardiac surveillance among adult survivors of childhood cancer essential

Yu A, Liu, JE. Biomed Res Int 2016

Abnormal GLS - Clinical Implications

- Increased risk of developing major adverse cardiac events and cancer therapeutic related cardiac dysfunction
- Warrant close surveillance for signs/symptoms of cardiac dysfunction
- Optimize existing cardiovascular risk factors
- Consider evaluation of underlying cardiac disease as clinically indicated

Role of GLS in Clinical Decision Making for Evaluation of Cancer Therapy Related Cardiac Dysfunction



*Marker of increased risk. Consider contributing pathology (HTN, CAD, infiltrative disease). Optimize existing CV risk factors, consider cardioprotective medications

Strain in Cardio Oncology: Limitations

- Prognostic GLS thresholds for CTRCD remain uncertain; prospective studies need to be performed to verify.
- Need to establish the incremental prognostic value of strain for predicting outcome such as clinical HF and move beyond the focus on a LVEF based definition of CTRCD.
- Using vendor-specific acquisition and analysis for sequential follow-up still preferred; though inter-vendor variability much improved since ASE/EACVI task force to standardize strain imaging between vendors
- Impact of hemodynamics on the variability of strain measurements during follow-up.

JACC: CARDIOONCOLOGY VOL. 2, NO. 5, 2020

ASE American Society of Echocardiography
Sound Saves Lives

PRIMERS IN CARDIO-ONCOLOGY

Strain Imaging in Cardio-Oncology

Jennifer E. Liu, MD,[a,b] Ana Barac, MD, PhD,[c] Paaladinesh Thavendiranathan, MD, SM,[d] Marielle Scherrer-Crosbie, MD, PhD[e]

EBAC

ABIM CME MOC ACCREDITED

Role of GLS in Cardio-Oncology:

- Sensitive for detecting subclinical LV dysfunction; reduction in GLS precedes a fall in LVEF.
- More reproducible with less variability when monitoring myocardial function during cancer treatment.
- Stronger predictor of heart failure and overall mortality
- Particularly useful in cases with borderline LVEF providing additional predictor of risk.

Strain imaging should be an integral part of comprehensive cardio oncology echocardiography study

Thank You!

liuj1234@mskcc.org