Early detection of cardiac dysfunction by echocardiography in cancer patients undergoing chemotherapy

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OVERVIEW

- How chemotherapies cause cardiotoxicity?
- Role of echocardiography for early detection
- Studies review
- Recommendation

How chemotherapies cause cardiotoxicity?

- The most common adverse effect is cardiotoxicity which may compromise the clinical effectiveness of chemotherapy, affecting the patient's survival and quality of life independently of the oncological prognosis.
- 2 types of cardiac toxicities, type I which is more serious and result in permanent damage to the myocardium and type II which is usually reversible.
- Chemotherapies varies in their incidence of inducing cardiomyopathy, and the onset which may occur acutely (during or shortly after treatment), sub-acutely (within days or weeks after completion of chemotherapy) or chronically (weeks to months after drug administration)

Douraid K. Shakir[a] and Kakil I Rasul[b,c] **Chemotherapy Induced Cardiomyopathy: Pathogenesis, Monitoring and Management,** 10.4021/jocmr2009.02.1225

How chemotherapies cause cardiotoxicitv?

Chemotherapy related cardiac dysfunction

TYPE I e.g. Doxorubicin	TYPE II e.g. Trastuzumab
Cellular death Damage starts with first administration	Cellular dysfunction
Biopsy changes	No typical biopsy changes
Cumulative dose related	Not cumulative dose related
Permanent damage (Myocyte death)	Predominately reversible (Myocyte dysfunction)
Risk factors	Risk factors
Prior/concurrent radiotherapy	Prior/concurrent anthracycline
Combination chemotherapy	Paclitaxel
Age	Age
Previous cardiac disease	Previous cardiac disease
Hypertension	Obesity (BMI > 25)

Douraid K. Shakir[a] and Kakil I Rasul[b,c] **Chemotherapy Induced Cardiomyopathy: Pathogenesis, Monitoring and Management,** 10.4021/jocmr2009.02.1225

How chemotherapies cause cardiotoxicity?

- Cardiac events associated with chemotherapy may consist of
  - Mild blood pressure changes,
  - Thrombosis
  - Electrocardiographic (ECG) changes
  - Arrhythmias
  - Myocarditis
  - Pericarditis
  - Myocardial infarction
  - Cardiomyopathy
  - Cardiac failure (left ventricular failure), and congestive heart failure (CHF)

Role of Echocardiography for early detection of cardiac events

Saint Luke's Mid American Heart Institute

A 46 year-old woman was initially diagnosed with right sided breast cancer

Treated with multiple chemotherapeutic agents including adriamycin and trastuzumab

Acute systolic heart failure, with NYHA class IV symptoms and a LVEF= 10%.

She required several days of inpatient treatment for parenteral diuresis, and initiation of a low dose betablocker and an angiotensin converting enzyme inhibitor

Her left ventricular systolic dysfunction was attributed to chemotherapy related cardiotoxicity.

Several months later, her left ventricular ejection fraction normalized, and her heart failure symptoms abated.

• Echocardiographic Myocardial Strain Imaging for Early Detection of Cardiotoxicity in Patients Receiving Potentially Cardiotoxic Chemotherapy. American society of echocardiography. Up to date.

Role of Echocardiography for early detection of cardiac events

A CASE IS NOT RARE!

15% incidence of heart failure and/or cardiomyopathy at 5 years following initiation of an anthracycline plus trastuzumab (1)

40% prevalence of congestive heart failure in women aged 66 to 70 years at 120 months following initiation of adjuvant anthracycline therapy (2)

In older women diagnosed with breast cancer, cardiovascular disease is actually the leading cause of death (3)

Up to 28% of women may manifest cardiotoxicity following treatment with trastuzumab (4), and prescribing information recommendations (5) that patients undergo echocardiography at baseline, and then every 3 months while on therapy, and every 6 months for at least 2 years following completion of trastuzumab, monitoring is suboptimal in a large proportion of patients (6).

1. Bowles EJ et al. Risk of heart failure in breast cancer patients after anthracycline and trastuzumab treatment: a retrospective cohort study. J Natl Cancer Inst 2012;104:1293-1305.
2. Pinder MC et al. Congestive heart failure in older women treated with adjuvant anthracycline chemotherapy for breast cancer. J Clin Oncol 2007;25:3808-3815.
3. Patnail JL et al. Cardiovascualr disease competes with breast cancer as the leading cause of death for older females diagnosed with breast cancer: a retrospective cohort study. Breast Cancer Research 2011;13:R64.
4. McArthur HL and Chia S. Cardiotoxicity of trastuzumab in clinical practice. N Engl J Med 357;94-95.
5. Herceptin Prescribing Information. Available at: http://www.gene.com/download/pdf/herceptin_prescribing.pdf accessed August 21, 2015.
6. Chavez-MacGregor M et al.Cardiac monitoring during adjuvant trastuzumab based chemotherapy among older patients with breast cancer. J Clin Oncol 2015;33:1-10.

Role of Echocardiography for early detection of cardiac events

Three major roles of echocardiography:

- Echocardiography can ensure that patients do not already have impaired cardiac function.
- During chemotherapy, cardiovascular ultrasound can monitor ventricular function to exclude chemotherapy induced dysfunction.
- During follow up treatment, cardiovascular ultrasound can determine if new symptoms are potentially due to cardiac disease.

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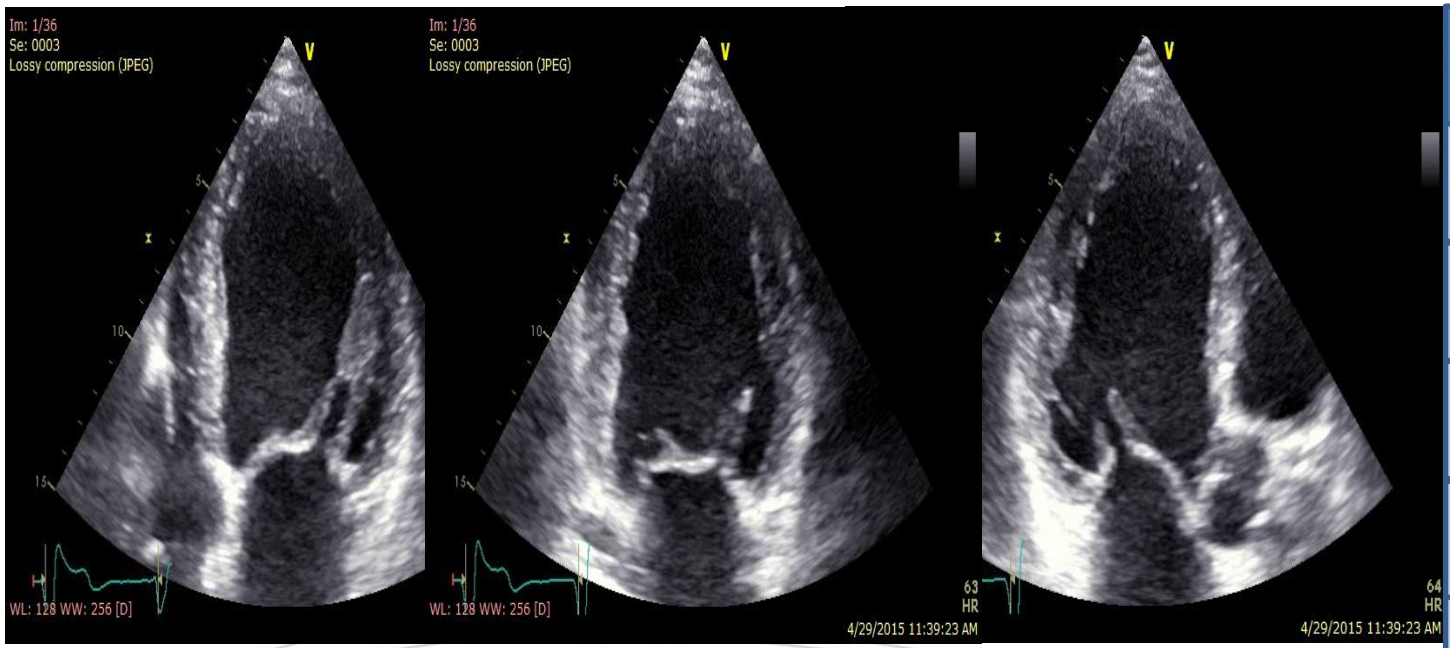
Role of Echocardiography for early detection of cardiac events

- Is important for modification in the chemotherapy regimen, either by increasing the interval between doses or reducing the total cumulative dose of a potentially toxic agent.
- LV function?:
  - EF Teichholz?
  - EF Simpsons?
  - EF Contrast enhanced image echo?
  - EF 3D?
  - Speckle tracking?

• Echocardiographic Myocardial Strain Imaging for Early Detection of Cardiotoxicity in Patients Receiving Potentially Cardiotoxic Chemotherapy. American society of echocardiography. Up to date.

Role of Echocardiography for early detection of cardiac events

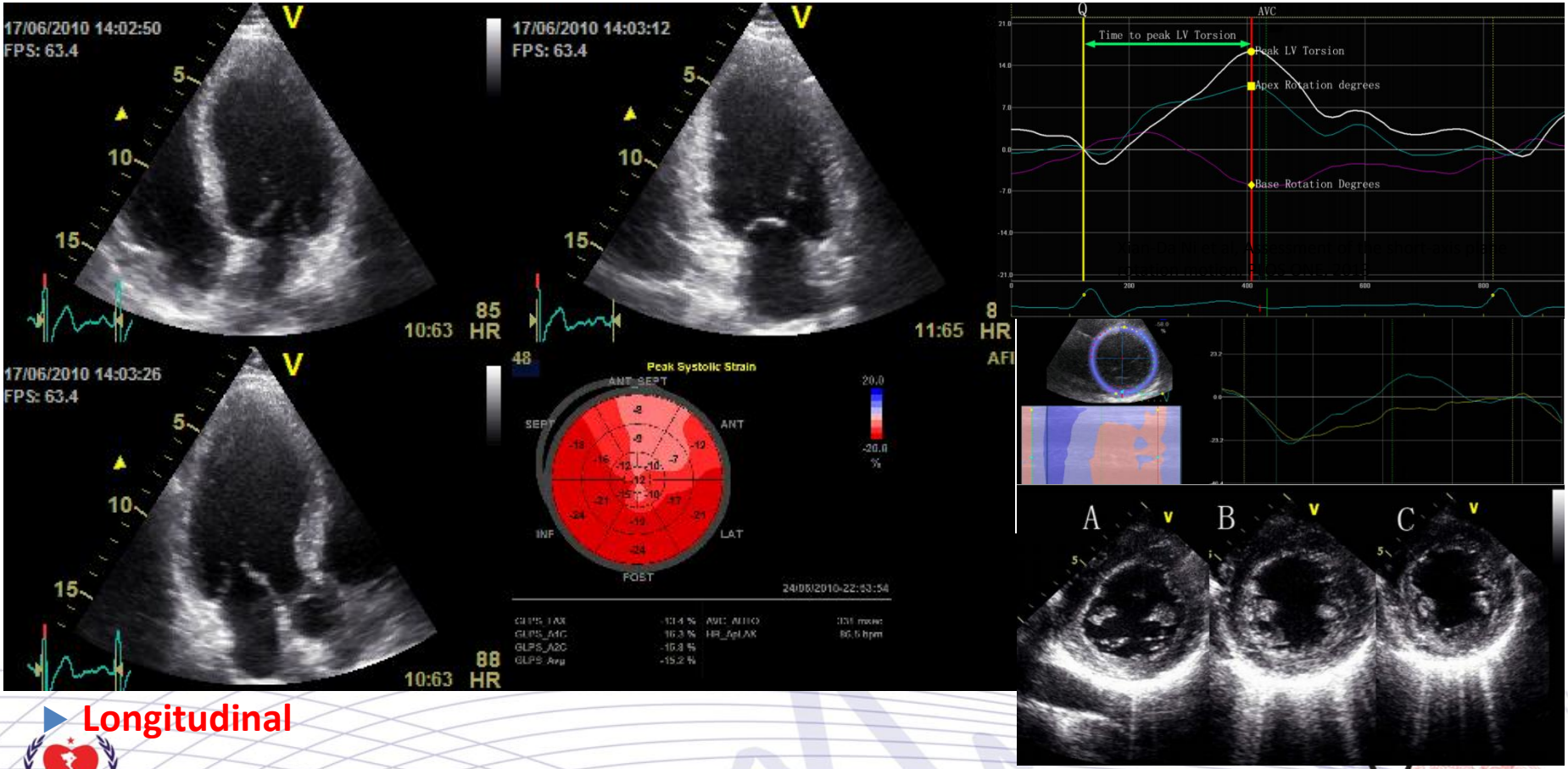
- Speckle tracking is realizable:



- 2D image quality
- Frame rate
- Depth and width
- Probe positioning
- Foreshortened
- Cardiac rhythm EKG

Role of Echocardiography for early detection of cardiac events

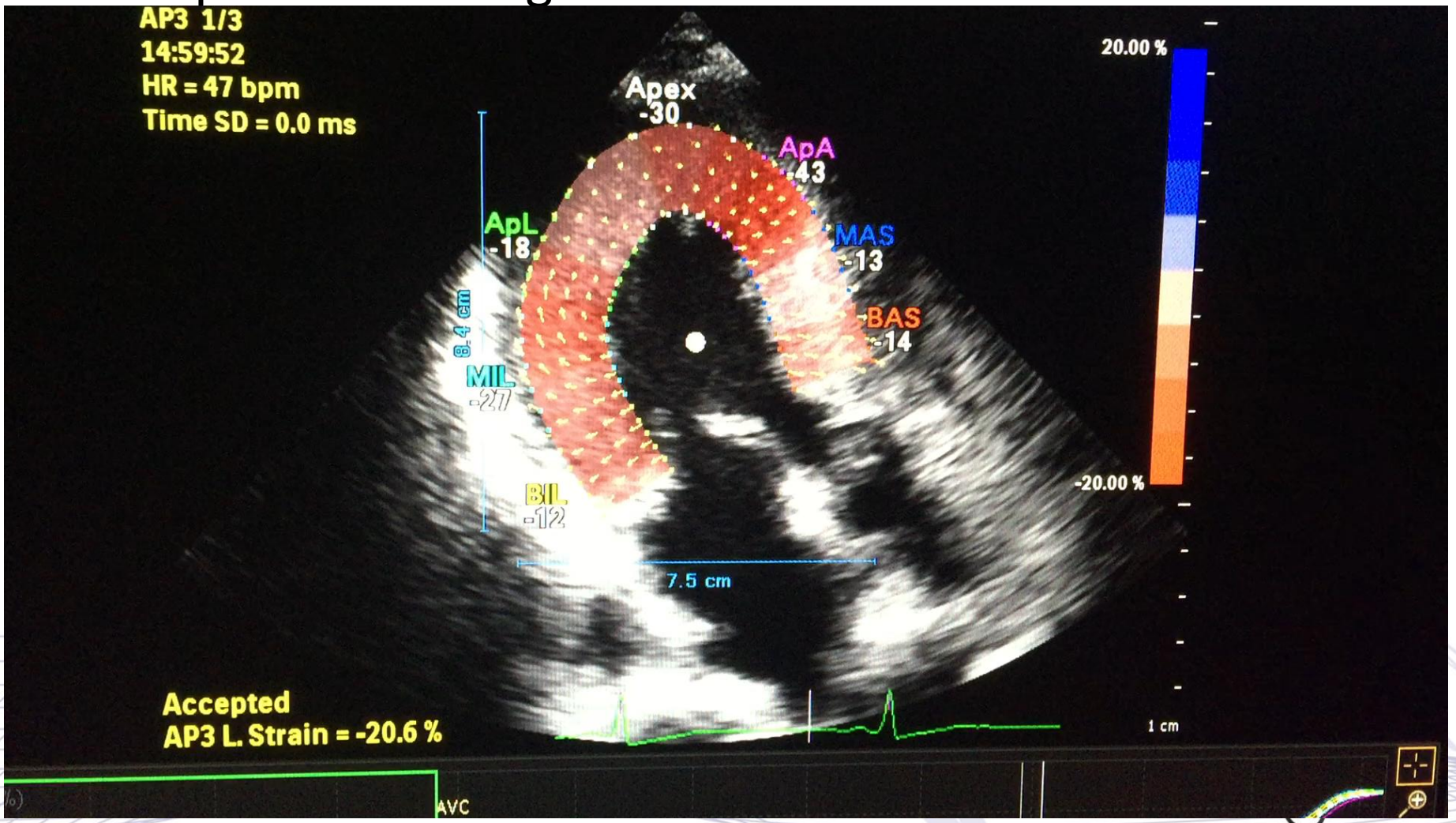
- Speckle tracking is realizable:



Longitudinal

Role of Echocardiography for early detection of cardiac events

- Speckle tracking is realizable:



Role of Echocardiography for early detection of cardiac events

- Speckle tracking is helpful:
  - Stage A= at high risk for heart failure, but without structural heart disease or symptoms,
  - Stage B = structural heart disease but without signs or symptoms of heart failure,
  - Stage C = structural heart disease with prior or current symptoms of heart failure, and
  - Stage D = refractory heart failure.
  - Currently, cardiotoxicity in patients receiving chemotherapy is typically diagnosed in Stage B to C. Myocardial strain imaging offers the potential to diagnose cardiotoxicity much earlier, in Stage A.

- Echocardiographic Myocardial Strain Imaging for Early Detection of Cardiotoxicity in Patients Receiving Potentially Cardiotoxic Chemotherapy. American society of echocardiography. Up to date.

Role of Echocardiography for early detection of cardiac events

Authors/year of publication	Subject (n)	Time of Echocardiography	%Δ GLS reduction/below of	Reference
Thavendiranathan and colleagues, 2014	Systematic review 1504 patients	During or after cancer chemotherapy for 3 clinically relevant scenarios.	10-15% relative	. J Am Coll Cardiol 2014; 63:2751-2768.
Mornos et al, 2013	74 patients anthracyclines	Pre, post and at 6, 12, 24 and 52 weeks.	13.1% relative at 6 weeks => cardiotoxicity at 24 to 52 weeks	Can J Physiol Pharmacol 2013;91:601-607.
Negishi and colleagues, 2013	81 patients trastuzumab or doxorubicin	Prior to therapy and at 6 and 12 months	≥ 11% relative => toxicity at 12 months	J Am Soc Echocardiogr 2013:26:493-498.
Baratta et al, 2013	36 patients trastuzumab or doxorubicin	Baseline, 2, 3, 4 and 6 months after initiation of therapy	≥ 15% relative at 3 months (sen 86%, spe 86%) => toxic	Rev Argent Cardiol 2013;81:151-158.
Sawaya et al, 2012	81 patients anthracycline or trastuzumab	Baseline, and at 3, 6, 9, 12, and 15 months.	Below of 19% => toxicity	Circ Cardiovasc Imaging 2012;5:596-603.

Echocardiographic Myocardial Strain Imaging for Early Detection of Cardiotoxicity in Patients Receiving Potentially Cardiotoxic Chemotherapy. American society of echocardiography. Up to date.

Authors/year of publication	Subject (n)	Time of Echocardiography	% Absolute GLS reduction/below of	Reference
Sawaya and colleagues, 2011	43 patients anthracycline or trastuzumab	Baseline and at 3 and 6 months	>10% at 3 months => cardiotoxicity at 6 months	Am J Cardiol 2011:107:1375-1380
Fallah-Rad, 2011	42 patients anthracycline or trastuzumab	Baseline, and at 3, 6, 9, and 12 months	ΔGLS ≥2.0 % (Sen 79%, Spe 82%) => subsequent cardiotoxicity	J Am Coll Cardiol 2011;57:2263-2270.
Hare et al	35 patients anthracycline or trastuzumab	baseline, post, and at 3 months	A > 1 standard deviation drop in global longitudinal strain rate predicted toxicity at of 22 ± 6 months.	Am Heart J; 158:294-301
Mavinkurve-Groothuis	60 patients anthracycline.	Baseline, and at 10 weeks and 12 months	No carditoxicity	Eur Heart J Cardiovasc Imaging 2013;14:562-569.
Le T.T et al, 2017	26 patients Anthracycline	Baseline, at 3 months	Significant GLS reduction (max Δ = 2.9%, = 14% relative) 3/26 below of 19%)	Journal of Vietnamese Cardiology, Volume 80, 2017.

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Role of Echocardiography for early detection of cardiac events

GLS percentage of reduction in acute leukemia patients undergoing anthracycline with GLS > -19%

Patients	GLS Baseline	GLS 3 months	Δ GLS	% reduction
1	-20,8%	-18,1%	2.7	13%
2	-20,3%	-18,7%	1.6	8%
3	-21,3%	-18,4%	2.9	14%

Speckle tracking to detect early systolic dysfunction of left ventricular: a study on acute leukemia patients with Anthracycline treatment. Le T.T, Duong T.Giang, Tran T.K.My, Nguyen T.B.Yen, Journal of Vietnamese Cardiology, Volume 80, 2017.

Recommendations for Strain Imaging in Cardio-Oncology

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

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

Keywords: Chemotherapy, Doxorubicin, Trastuzumab, Left ventricular dysfunction, Three-dimensional

Recommendations for Strain Imaging in Cardio-Oncology

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)

ACE, Angiotensin-converting enzyme.

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Recommendations for Strain Imaging in Cardio-Oncology

Table 2 Recommended cardio-oncology echocardiogram protocol

Standard transthoracic echocardiography
- In accordance with ASE/EAE guidelines and IAC-Echo

2D strain imaging acquisition
- Apical three-, four-, and two-chamber views
  - Acquire ≥3 cardiac cycles
- Images obtained simultaneously maintaining the same 2D frame rate and imaging depth
  - Frame rate between 40 and 90 frames/sec or ≥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 bull's-eye plot

2D strain imaging pitfalls
- Ectopy
- Breathing translation

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Recommendations for Strain Imaging in Cardio-Oncology

3D imaging acquisition

- Apical four-chamber full volume to assess LV volumes and LVEF calculation
- Single and multiple beats optimizing spatial and temporal res-olution

Reporting

- Timing of echocardiography with respect to the IV infusion (number of days before or after)
- Vital signs (BP, HR)
- 3D LVEF/2D biplane Simpson's method
- GLS (echocardiography machine, software, and version used)
- In the absence of GLS, measurement of medial and lateral s′ and MAPSE
- RV: TAPSE, s′, FAC

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Recommendations for Strain Imaging in Cardio-Oncology

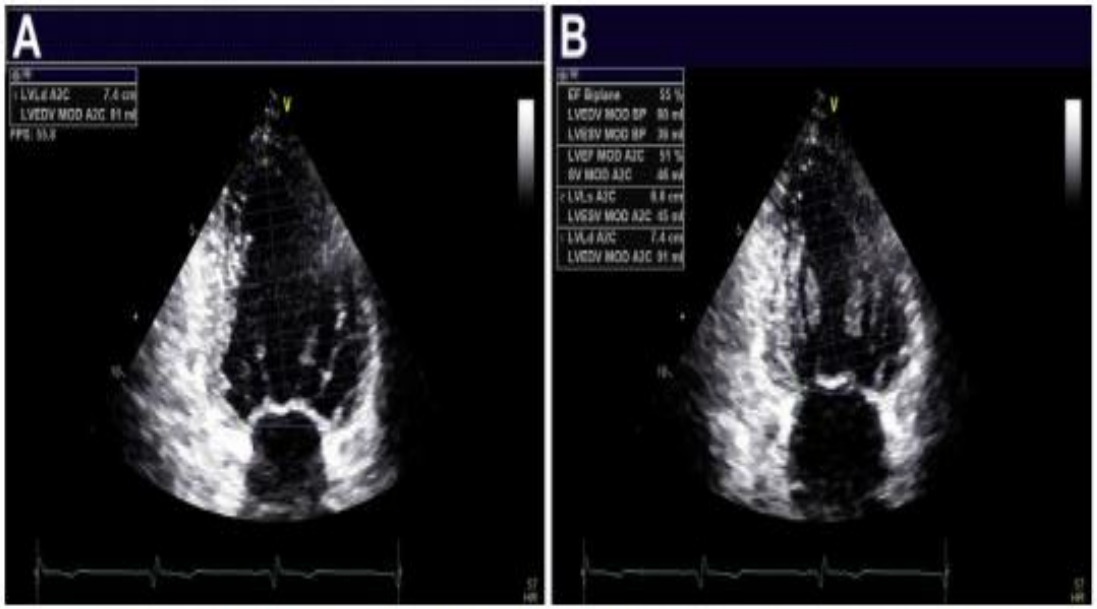

Figure 1 Calculation of LVEF using the biplane Simpson's method. **(A)** Apical two-chamber view obtained at end-diastole. **(B)** Apical two-chamber view obtained at end-systole.

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Recommendations for Strain Imaging in Cardio-Oncology

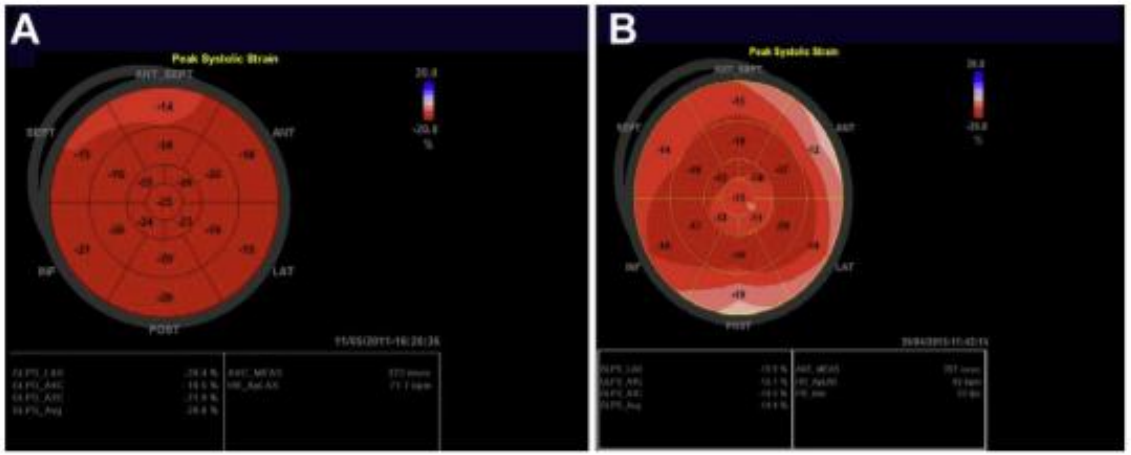

Figure 9 Bull's-eye plot showing GLS of the patient shown in Figure 8. **(A)** GLS and regional longitudinal strain at baseline. **(B)** GLS and regional longitudinal strain 3 months during trastuzumab-based therapy after anthracyclines. GLS has decreased from −20.6% to −14.4% (30% decrease). The decrease in GLS is therefore considered of clinical significance (>15% vs baseline).

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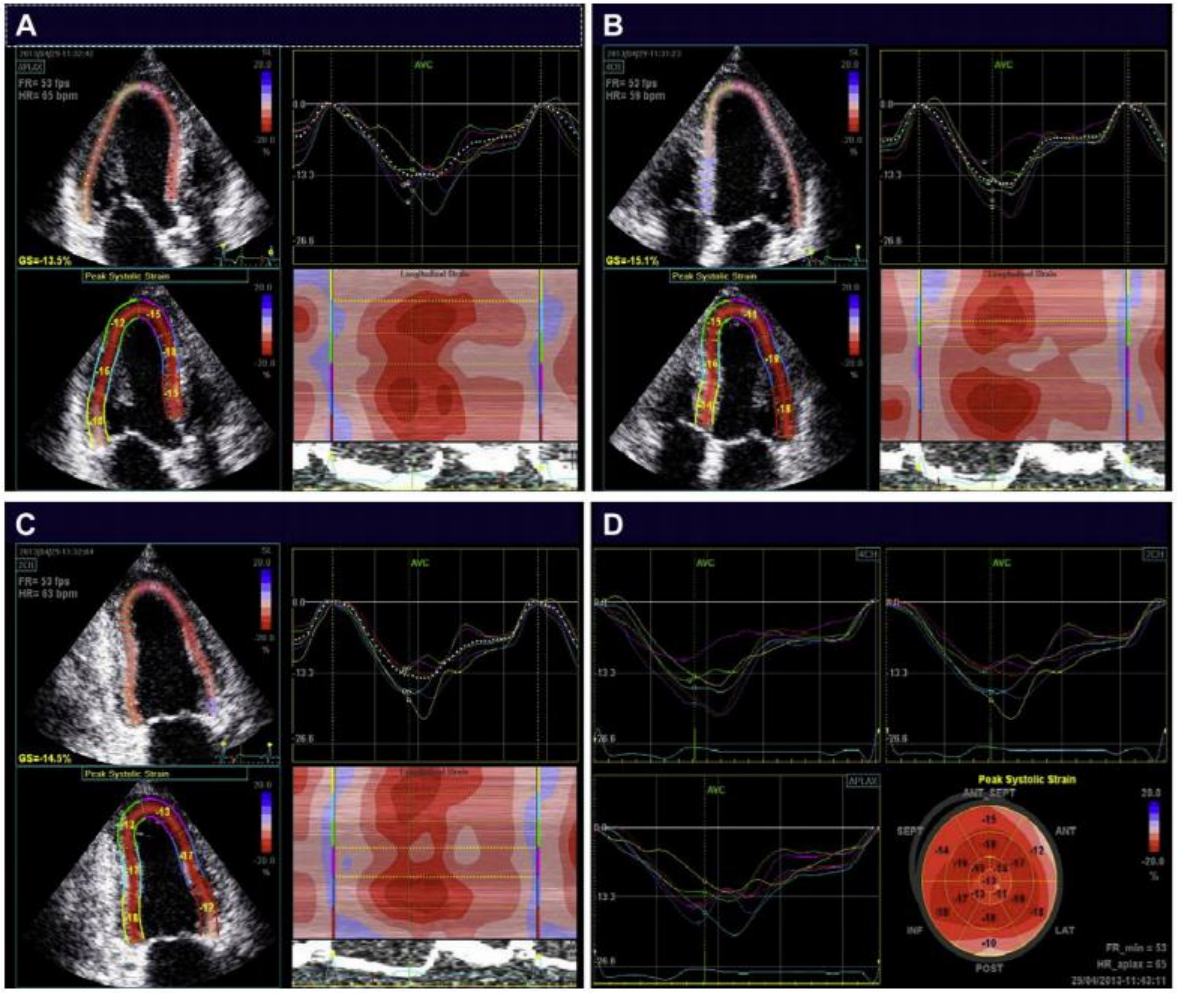
Recommendations for Strain Imaging in Cardio-Oncology



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Example

Saint Luke's Mid American Heart Institute

A 54 year-old woman, breast cancer, trastuzumab

Normal GLS at baseline (-24%)

After 12 doses: -17.8% (>-19%, % of reduction = 23%). Normal EF!

Beta-blocker, ACE inhibitor, and close clinical monitoring.

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CONCLUSION

1. Two types of cardiotoxicity by chemotherapy
2. Speckle tracking is a standardized technique to early detect cardiotoxicity.
3. Percentage reduction of GLS > 10% => early stage of cardiotoxicity
4. Percentage reduction of GLS > 15% => clinical significance of cardiotoxicity => require treatment
5. Beta-block, ACE inhibitor, consider diuretic are suitable for treatment.

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THANK YOU